A CLINICAL STUDY OF PERIPHERAL NEUROPATHY IN BUNDELKHAND REGION

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<u>C E R T I F I C A T E</u>

This is to certify that the work entitled "A CLINICAL STUDY OF PERIPHERAL NEUROPATHY IN BUNDELKHAND REGION", which is being submitted as a thesis for M.D.(Medicine) Examination, 1993 of Bundelkhand University, has been carried by Dr. Ravindra Nath Mishra in the department of Medicine, M.L.B. Medical College, Jhansi.

He has put in the necessary stay in the department as per university regulations.

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CERTIFICATE

This is to certify that the work entitled "A CLINICAL STUDY OF PERIPHERAL NEUROPATHY IN BUNDELKHAND REGION", which is being submitted as a thesis for M.D.(Medicine) Examination, 1993 of Bundelkhand University, has been carried out by Dr. Ravindra Nath Mishra under my direct supervision and guidance. The observations recorded have been checked and verified by me from time to time.

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C O N T E N T S

I N T R O D U C T I O N

INTRODUCTION

Peripheral neuropathy is a general term indicating disorder of peripheral nerve of any cause. Therefore, knowing that a peripheral neuropathy is present in a particular patient should instigate a search for its basis.

Polyneuritis (polyneuropathy) is a clinical syndrome of which the essential feature is simultaneous impairment of function of many peripheral nerves, often resulting in symmetrical flaccid muscular weakness, and usually also sensory abnormalities, affecting as a rule the distal more than the proximal segments of the limbs, and sometimes also involving the cranial nerves. Polyneuropathy thus defined has many causes, which may operate in many different ways and may involve different parts of the peripheral nerves. Among the causes are numerous endogenous and eoxgenous toxins, acute inflammatory processes, which directly attack the nerves, ischaemia, and many metabolic disorders including vitamin deficiency.

Peripheral neuritis was recorded by Lettsom (1789) and an epidemic in Paris was described by Robert Graves (1829). Todd first conceived that the terminal branches of the peripheral nerves might undergo degeneration and this was demonstrated pathologically by Dumenil in 1864. Joffroy in 1879 contributed to the

classification of polyneuritis and Grainger Stewart gave it the name multiple symmetrical peripheral neuritis in 1881. Korsakow described the mental changes sometimes associated with alcoholic polyneuritis in 1889.

As Simpson (1962) pointed out, except in the case of leprosy and the autoimmune neuropathies, true inflammation in the peripheral nerves is relatively uncommon and most such disorders are more correctly termed neuropathy.

The electrophysiological, nerve conduction, and pathological studies have provided more information regarding peripheral neuropathy. The major pathological processes are following :

1. Wallerian degeneration (the response to transection).
2. Axonal atrophy and degeneration (Axonopathy).
3. Segemental demyelination(myelinopathy).
4. Primary disorders of nerve cell bodies(Neuronopathy).

In demyelinating (the myelin sheath, and/or Schwann cells are attacked by disease) neuropathies, nerve conduction is usually markedly delayed, while in axonal degenerations, there may be no conduction at all, or, if denervation is partial, the surviving axons conduct at a normal rate but the amplitude of evoked muscle or sensory potentials is reduced since fewer axons respond.

While many forms of polyneuropathy affects both sensory and motor fibres, some appears to involve motor

fibres selectively and others sensory fibres, while it is also evident that sometimes heavily myelinated, rapidly conducting fibres are predominantly involved, while in other cases finely myelinated or even unmyelinated fibres are attacked. Some processes which involve the axon primarily seem to involve its entire length, others begin distally (dying-back-neuropathy). The factors which determine such selective involvement of Schwann cells, myelin, axons and different classes of fibres are still poorly understood (Bradley, 1974; Dyck, Thomas and Lambert, 1983).

Neuropathic clinical syndromes encountered have variations in the rate of evolution, fluctuations in the course, the eventual degree of severity, the presence or absence of positive motor or sensory symptoms, the symmetry of features and their distribution in terms of proximal versus distal, arms versus legs, motor versus sensory, the relative proportion of dysfunction attributable to large fibres deficit and to small fibre deficit and the determination, mainly by electrodiagnostic examination of axonal versus demyelinating processes.

Peripheral neuropathy is known to be present with more than 100 associations (drugs,toxins, metabolic disorders, deficiency states, dysimmune states, connective tissue disorders, trauma, ischaemia, genetically determined disorders etc.). A significant number of patients can be detected clinically. A clinical study performed by

Dube et al (1969) as neurological manifestations in diabetes, had shown clinical neuropathy in 43 cases out of 80 cases of diabetes mellitus. Another clinical study was performed by Kaur et al (1982) supported by laboratory data, electromyography and sural nerve biopsy examination, restricted to patients admitted to a teaching hospital in the capital city of Chandigarh. In 3 years 570 cases were seen and constituted 8.5/1000 hospital admissions. Patients with diabetic neuropathy (65.6%) and leprosy (14.4%) formed the majority.

Keeping the above informations in mind, a clinical study of peripheral neuropathy in Bundelkhand region, was done with following aims:

1. Clinical study of patients, presenting with features of peripheral neuropathy and investigations to find out possible aetiological factors(associations) in such cases.

2. To detect the presence of asymptomatic peripheral neuropathy in diseases known to cause this complication viz. diabetes, leprosy, patient getting neurotoxic drugs etc.

R E V I E W   O F   L I T E R A T U R E

REVIEW OF LITERATURE

The following classification includes the important causes :

1. TOXIC SUBSTANCES
   a. Metals : Antimony, arsenic, bismuth, copper, lead, mercury, phosphorus, thallium.
   b. Drugs : Amiodarone, chloroquine, cytotoxic agents including vincristine sulphate, Dapsone, disulfiram, emetine, ethionamide, glutethimide, hydrallamine, immune sera, indomethacin, isoniazid metronidazole, nitrofurantoin, phenytoin, step-tomycin, sulphanilamide.
   c. Organic chemicals and other toxic substances
      Acrylamide, anilline, bush tea, calcium carbimide, carbon monoxide, carbon disulphide, carbon tetra-chloride, chloral, D.D.T. dinitrobenzole, ethylene oxide, parathion, tetrachloroethane, triorthocresyl phosphate.

2. DEFICIENCY, METABOLIC AND HAEMATOLOGICAL DISORDERS
   Beri-beri, chronic alcoholism, COPD, folic acid deficiency, liver disease, chronic disease of(including coeliac disease) or operations upon the GIT, pellagra, protein calorie malnutrition, pregnancy, tropical neuropathy, vitamin B_{12} neuropathy, Acromegaly, diabetes, hyperinsulinism, myxoedema, porphyria,

Neuropathy in A alpha and A beta lipoproteinaemia, in dysglobulinaemia, Benign monoclonal gammopathy and various paratproteinaemias.

Neuropathy in polycythaemia vera, leukaemia, multiple myeloma and haemorrhagic disorders.

3. <u>INFECTIVE CONDITIONS</u>

a. <u>Local Infection of nerves</u> : Brucellosis, leprosy, leptospirosis, infective mononucleosis, very rarely syphilis.

b. Polyneuritis complicating acute or chronic infections, dysentry, influenze, malaria, measles, mumps, paratyphoid, puerperal sepsis, scarlet fever, septicaemia, syphillis, tuberculosis, typhoid, typhus.

c. Infections with organisms whose exotoxins have an affinity for the peripheral nerves.
- Diphtheria, dysentry, tetanus.

4. <u>Post Infective (? Allergic) Polyneuropathy</u> :

- Acute post infective polyadiculoneuropathy (Guillain Barre Syndrome).
- Some cases of subacute and chronic polyneuropathy.
- ? Recurrent polyneuropathy.

5. <u>Trauma</u> : Physical injury and nerve entrapment electric shock, cold and radiation injury.

6. Ischaemic Neuropathies : Neuropathies due to ischaemia or infarction of peripheral nerves as in peripheral vascular disease.

7. Connective tissue and allied disorders : Giant cell arteritis, polyarteritis, nodosa, rheumatoid polyneuritis, sarcoidosis, SLE, progressive systemic sclerosis, other vascular neuropathies including peripheral vascular disease.
8. Genetically determined polyneuropathy : Peroneal muscular atrophy, Roussy Levy Syndrome, Progressive hypertrophic polyneuritis of Dejerine and Sottas, Refsum's disease, hereditary neuropathy with liability to pressure palsies.

Neuropathy in metachromatic leucodystrophy, Krabbe form of diffuse sclerosis and other leucodystrophies, storage disorders, primary amyloidosis, porphyria, Fabry's disease. A Alpha and A beta lipoproteinaemia and various other obscure varieties of hereditary neuropathy including neuropathic arthrogryposis multiplex congenita, so called globular neuropathy, giant axonal neuropathy, neuropathy with optic atrophy, nerve deafness and or paraproteinaemias.

9. Polyneuropathy of obscure origin : Recurrent polyneuritis, chronic progressive polyneuritis, Carcinomatous neuropathy and other paraneoplastic neuropathies, congenital hypomyelination neuropathy, neuropathies of undetermined causes.

TOXIC SUBSTANCES : METALS

LEAD

It has long been known that in lead neuropathy, the muscles paralysed are usually those most used in the patient's occupation (Hunter, 1978). Fullerton (1966) showed that this heavy metal produces both axonal degeneration and demyelination in the peripheral nerves of guinea-pigs. Recent work suggests that there is a direct toxic effect upon Schwann cells (Dyck, O'Brien and Ohnishi, 1977).

It is characteristic of lead neuropathy that it is predominantly motor and sensory symptoms and signs are usually slight or absent. This condition usually affects the extensor muscles of the wrist and fingers, as a rule bilaterally, though the right side may suffer alone, especially in right handed individuals. Wrist and finger drop occur and the loss of synergic extension of the wrist causes weakness of flexion of fingers. The brachioradialis often escapes and so, as a rule, does abductor pollicis longus. If the upper arm is involved the spinati, deltoid, biceps, brachialis and brachioradialis muscles may be affected. This distribution of paralysis is seen in those using these muscles repeatedly as for example, in men making batteries. The lower limbs are occasionally affected, the muscles paralysed being those supplied by the common peroneal nerve, with the exception of tibialis anterior, which often escapes. Rarely the

TABLE : Clinical syndromes of drug induced neuropathy and drugs implicated.

Clinical presentation	Antimicrobial drugs	Antineoplastic drugs	Cardiovascular drugs	Hypnotics & psychotropics	Antirheumatic drugs	Other drugs
Sensory neuropathy	Ethionamide Chlorumphenicol Diamines Thiamphenicol	Procarbazine nitrofurazone				Calcium carbimide sulfoxone ergotamine propylthiouracil
Paraesthesiae only	Colistin Streptomycin nalidixic acid	Cytarabine	Propanol	Phenelzine		Sulthiame Chlorpropamide methysergide
Sensorimotor neuropathy	Isoniazid Ethambutol Streptomycin nitrofurantoin clioquinol metronidazole	Vincristin podophyllum chlorumbucil	Perhexiline hydrallazine amiodarone disopyramide clofibrate	thalidomide methaqualone glutethimide amitryptyline	Gold indomethacin colchicine chloroquine Phenylbutazone	phenytoin disulfiram carbutamide tolbutamide chlorpropamide methimazole
Predominantly motor	Sulphonamides amphotericin			imipramine		dapsone
Localised neuropathies	amphotericin penicillin	mustine ethoglucid				Anticoagulants

Source : B.M.J., 10th March, 1979.

weakness and wasting is so widespread that it stimulates progressive muscular atrophy but the evidence that lead intoxication plays a part in the pathogenesis of motor neurone disease is unconvincing.

DRUG INDUCED PERIPHERAL NEUROPATHY

Awareness of the possibility of drug induced peripheral nerve damage is important because of the over increasing number of therapeutic agents being introduced into clinical practice and prompt recognition of this complication is imperative if severe neurological deficits are to be avoided. The incidence of drug induced peripheral neuropathy is difficult to establish, since the association with drug treatment is not always recognised, mild forms are easily overlooked and sub-clinical disorders are probably more frequent than is generally appreciated.

The underlying disease may itself modify the susceptibility to neuropathy, for example, patients with lymphoma develop vincristine neuropathy more often than those with other malignancies. Others, who may be predisposed include patients with cancer, diabetes, alcoholism or vitamin deficiency, conditions in which the peripheral nerves may already be affected.

Symptoms of autonomic dysfunction may be prominent particularly in patients with vincristine neuropathy. Localised damage to peripheral nerves or a nerve plexus may result from intramuscular injections,

intraarterial infusions of cytotoxic agents or haemorrhage in patients in whom anticoagulant treatment is poorly controlled. Brachial plexus neuropathy may occasionally develop after intramuscular injections of penicillin, presumably on an allergic basis. Certain cranial nerves may also be affected, either selectively or as part of a more generalised neuropathy, the optic, trigeminal and eighth cranial nerves being most often affected.

ANTIMICROBIAL AGENTS

Some of the antituberculosis agents in use may cause peripheral or optic nerve damage. Isoniazid produces a mixed sensorimotor peripheral neuropathy that may be prevented by giving vitamin B_6 supplements. The neuropathy is more likely to develop in slow acetylators, who have higher blood levels of free isoniazid for a longer time than rapid acetylators. The amount of acetyl transferase in the liver is genetically determined, slow inactivation (low acetyl transferase) being an autosomal recessive trait. Isoniazid induces pyridoxine deficiency by inhibiting pyridoxal phosphate kinase and also combines with pyridoxal phosphate. Administration of pyridoxine prevents the development of neuropathy without interfering with antitubercular action of isoniazid. The numbness and painful burning paraesthesiae occur in the extremities. Deep sensation is less affected. Distal

weakness with cramps and painful muscles occur at a later stage.

Ethambutol is less neurotoxic but may cause optic neuropathy, a mixed sensorimotor neuropathy or a predominantly sensory neuropathy.

Ethionamide, which is structurally related to isoniazid may rarely cause peripheral neuropathy, as may streptomycin after prolonged administration, although this is less frequent than the ototoxic effects of the drug.

Cases have been reported in which a symmetrical sensorimotor peripheral neuropathy developed during treatment with this drug and was shown to occur only in those with severe impairment of renal function (Ellis, 1962; Loughridge, 1962). Even in normal persons the drug may cause reduction in motor and/or sensory nerve conduction velocity (Toole et al, 1968), but clinical polyneuropathy is uncommon when the drug is given for short periods, if the renal function is unimpaired.

There are several reports of sensory neuropathy developing in patients treated with conventional doses of metronidazole for 6-24 weeks. Electrophysiological studies have shown that both sensory and motor nerve fibres may be affected. A sural nerve biopsy specimen from one patient showed axonal degeneration affecting both small and large diameter fibres. The neuropathy is reversible after withdrawal of the drug but recovery may be protracted.

Following high doses of metronidazole, encephalopathy and cerebellor ataxia have been described in addition to sensory neuropathy (Kusumi et al, 1980).

ANTINEOPLASTIC AGENTS

Vincristine sulphate, widely used for the treatment of leukaemia, lymphoma, medulloblastoma in childhood and of intracranial gliomas in adult life, has been found to produce sensorimotor polyneuropathy in many cases (Sandler, Tobin and Henderson, 1969; McLeod and Penny, 1969). Both sensory and motor nerves may be severely affected and the tendon reflexes are lost at an early stage. Postural hypotension and constipation due to autonomic disorders may be early symptoms. Electrophysiological studies have shown evidence of severe axonal damage affecting motor and sensory fibres, the reflex loss probably being due to damage to afferent fibres from the muscle spindles. Histological studies have shown severe axonal degeneration with only minor segmental demyelination. Several other cytotoxic drugs may cause peripheral nerve damage but are less neurotoxic than vincristine.

A predominantly sensory neuropathy may occur in patients treated with hydrallazine. Mild or subclinical neuropathy may occur in as many as 15% of patients taking the drug. This seems to be unrelated to the systemic lupus erythematosus - like syndrome induced by the drug and may be due to a disturbance of pyridoxine metabolism, since

hydrallazine is structurally related to isoniazide.

Peripheral neuropathy may occasionally develop in patients receiving amiodarone or disopyramide. Sensorimotor neuropathy has been described in a few patients following 400 mg per day of amiodarone for one or more years. Both axonal degeneration and segmental demyelination are present in nerves. Lysosomal dense bodies have been identified in Schwann cells and also in fibroblasts and perineural cells (Meier et al, 1979). Meier et al (1979) found that the iodine content of nerve and muscle was increased suggesting that the stored lipid was related to accumulation of the drug (which contains iodine) or its metabolite. The amiodarone neuropathy tends to be dose dependent (Martinez-Arizala et al, 1983).

Rarely peripheral nerves may be affected in patients with the typical painful myopathy caused by clofibrate.

HYPNOTICS AND PSYCHOTROPIC DRUGS

A predominantly motor neuropathy may occasionally develop in patients treated with imipramine and amitriptyline but such cases have not been studied fully. Reports of neuritis developing in patients receiving chlorprothixene and of acroparaestehsiae in those receiving phenelzine are difficult to evaluate. Sensory neuropathy has been described in patients addicted to glutethimide but is not a complication of conventional use of the drug.

ANTIRHEUMATIC DRUGS

Peripheral neuropathy occurs in 0.5-1% of patients with rheumatoid arthritis who have gold treatment. Motor disorders are prominant and sensory symptoms may be inconspicuous. An abrupt onset and rapid progression in some cases and associated facial diplegia and raised protein concentration in CSF may mimic acute post infective polyneuropathy. Few cases have been studied electrophysiologically or pathologically but axonal degeneration appears to be the main process.

Indomethacin has also been implicated to cause neuropathy. A report on four patients with sensorimotor neuropathy and two with sensory symptoms only suggested that the drug was responsible. EMG studies showed considerable slowing of motor conduction velocities in one case. Further studies are needed to determine the incidence of this complication.

A motor polyneuropathy, unaccompanied by symptoms or signs of sensory dysfunction, may develop in patients receiving treatment with chloroquine, usually in doses of 500 mg daily or more for one year or longer. Histological studies indicate that the muscle fibres are also affected as they commonly show striking vacuolation which appears to be due to the accumulation of glycogen. The nerve lesion seems to affect mainly the terminal axons and recovery is usually rapid after withdrawal of the drug (Gerard et al, 1973).

Peripheral neuropathy has been reported in patients treated with penicillamine, but less often than the myasthenic syndrome that develops in some patients treated with the drug. The mechanism of the neuropathy may be related to that caused by isoniazid, since penicillamine has an antipyridoxine effect.

Paraesthesiae and muscle weakness have been reported in some patients treated with phenylbutazone but are difficult to evaluate.

ANTICONVULSANTS

Patients receiving long term phenytoin treatment may develop a predominantly sensory polyneuropathy that is usually mild and rarely causes symptoms. The incidence of this complication is uncertain but signs of peripheral nerve disorders such as depression of tendon reflexes, are found increasingly often in patients receiving prolonged treatment. The electrophysiological studies have shown that subclinical lesions are common and that the neuropathy is of dying-back axonal degeneration type. The drug also has acute, reversible effects, particularly on slow conducting motor nerve fibres. There is no convincing evidence to show that any of the other commonly used anticonvulsants cause peripheral nerve damage.

OTHER DRUGS

Disulfiram causes a sensorimotor neuropathy with axonal degeneration and may also cause optic nerve damage.

These effects may be due to its neurotoxic metabolite carbon disulphide. A number of sulphones may also cause neuropathy. Dapsone may cause a subacute almost purely motor neuropathy, particularly after prolonged high dose treatment. Reduction of motor nerve conduction velocity is slight even in the presence of severe denervation, suggesting primary axonal pathology. Dapsone is acetylated by N-acetyl transferase, as is isoniazid. Koller et al (1977) found slow acetylation of isoniazid in one patient with dapsone neuropathy. Because of the rarity of the condition, it has not been established whether neuropathy only occurs in slow acetylators.

Neuropathy is a rare sequel of serotherapy, most often seen after the administration of antiserum in the treatment of tetanus and diphtheria. Nervous symptoms usually appear two or three days after the onset of serum sickness. The commonest lesion is radiculopathy, the fifth cervical spinal nerve being most often affected on one or both sides, with pain in the corresponding segmental distribution and paralysis of the relevant muscles, especially the deltoid. This syndrome is almost identical with that of 'shoulder girdle neuritis' (Neuralgic amyotrophy). Less often the whole brachial plexus is involved or a more diffuse polyneuropathy occurs. Optic neuritis has been described. Complete recovery usually occurs in from 1-18 months, though occasionally some muscular weakness persists.

ORGANIC CHEMICALS AND OTHER TOXIC SUBSTANCES

ORGANOPHOSPHATES (OP)

Practically all organophosphates are acetylcholinesterase inhibitors and have the expected acute toxic effects (Numba et al, 1971). No OP compounds in current use have caused peripheral neuropathy, following their use as insecticides. Occasional cases of neuropathy have followed suicide attempts, most commonly with trichlorphon (Hierons and Johnson, 1978). Tri_orthocresyl phosphate (TOCP), used in lubrication oil and as a degreaser has been responsible for most cases of OP neuropathy. Epidemics have followed accidental contamination of cooking oil (Smith and Spalding, 1959).

Intoxication has usually followed accidental ingestion of a single dose. There is latent interval of 1-3 weeks before the onset of neurological symptoms.

Paraesthesiae may occur at the onset but are always mild and other sensory changes are minimal or absent. Weakness progresses rapidly for some days. The relative involvement of peripheral and central motor pathways varies in different subjects. Spasticity and upper motor neuron weakness may be present at the onset or only become manifest as the peripheral nerves recover. Ankle reflexes are always absent but other tendon reflexes may be either absent or increased.

Normal motor nerve conduction velocity has been described in the presence of severe weakness in both humans and animals (Hierons and Johnson, 1978; Hern

1973). This is because large diameter fibres are not selectively affected. Sensory nerve action potentials may be reduced in amplitude or absent even when there is no significant sensory loss (Hierons and Johnson, 1978).

Treatment with atropine and cholinesterase reactivators (e.g. pralidoxime) have no influence on the development of neuropathy.

Organophosphate compounds act by inactivating the enzyme acetylcholinesterase and the clinical features are due to cholinergic crisis. The late complication of these insecticides is distal polyneuropathy (mostly motor), which usually develops after 2-3 weeks of taking the poison. Recently another neurotoxic syndrome known as "intermediate syndrome" is described (Wadia et al; Gadoth and Fisher; Senanayake and Karallidde, KK Samal and Sahu). This syndrome usually develops after 1-4 days of ingestion of the poison and is characterised by cranial nerve palsies, weakness of the proximal limb muscles, neck muscles, and respiratory muscles. Recovery usually occurs within 4-18 days and death if occurs, is due to respiratory paralysis. This intermediate syndrome or type-2 paralysis is not uncommon in India (Joshi and Sainani, 1987). The incidence was 15% in the series of Wadia et al. Atropine and certain oximes like PAM neither prevent nor have therapeutic effect on this syndrome.

DEFICIENCY, METABOLIC AND HAEMATOLOGICAL DISORDERS

ALCOHOLIC POLYNEUROPATHY

In chronic alcoholism, the deficiency of thiamine being due to a combination of defective diet, impaired absorption owing to gastrointestinal irritation and increased need caused by high calorie value of the alcohol. The pathological changes in affected nerves are identical with those of beri-beri (Novak and Victor, 1974). However, Behse and Buchthal (1977) reported findings which suggested that in addition to the deficiency of thiamine, there is a direct toxic action of alcohol on the peripheral nerves and this question is still not settled (Asbury and Johnson, 1978; Spencer and Schaumberg, 1980).

The changes are those of a predominantly axonal polyneuropathy of the dying back type (Prineas, 1970), involving the somatic peripheral nerves and some times the vagus and sympathetic nerves, sparing usually greater splanchnic nerve. The affected neurons show axonal degeneration especially at the periphery and chromatolysis is found in ganglion cells of the anterior horns and spinal dorsal root ganglia and ganglia of the motor neuclei of the cranial nerves.

Both motor and sensory symptoms affect predominantly the periphery of the limbs symmetrically. Sensory disturbances are usually prominent in the clinical picture. Tendon reflexes are diminished or lost. The sphincters are usually unaffected. The pupils tend to be contracted

and may react slugghishly to light. Nystagmus is common. The cranial nerves may be affected, the vagus being most often involved, with resulting tachycardia and impaired barroreceptor responses and the facial nerve next in frequency. Korsakow's psychosis, Wernicke's encephalopathy or alcoholic dementia may be present. Other manifestations of alcohol are often present.

NEUROPATHY IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

A mild sensorimotor, usually asymptomatic neuropathy has been demonstrated clinically and electrophysiologically in some patients with chronic obstructive pulmonary disease (Appenzeller, Parks and Mac Gee, 1968; Faden Mandoza and Flynn, 1981). In one study, the patients had muscle wasting and in some cases improvement followed treatment of the pulmonary disease and associated malnutrition, it seems likely that nutritional and metabolic disturbances were mainly responsible for the peripheral neuropathy. In another study, mild sensory neuropathy and no evidence of muscle wasting, an association with tobacco smoking was described and a toxic aetiology suggested (Faden, Mendoza and Flynn, 1981). However, it seems to be of little clinical importance because neuropathy has not been described as presenting or dominant clinical feature of any patient with COPD.

NEUROPATHY IN FOLIC ACID DEFICIENCY

Folate deficiency produced by malnutrition, malabsorption (as in steatorrhoea and intestinal blind

loop syndromes) or by the use of anticonvulsant drugs causes polyneuropathy in addition to myelopathy, haematological abnormalities and mental illness including dementia (Grant, Hoffbrand and Wells, 1965; Reynolds, Rothfeld and Pincus, 1973; Carney, 1967). In some such cases improvement was noted after the administration of folic acid, 5 mg three times daily. While the exact role of folate in the aetiology of neurological disorders remains uncertain, it is reasonable to estimate the serum folate in cases of unexplained polyneuropathy, myelopathy and dementia(Folate deficient with serum values of less than 2 ug/ml). The polyneuropathy due to folate deficiency is predominantly sensory (Martinez - Figueroa et al, 1980). The pathological features in the peripheral nerve are those of axonal degeneration (Bischoff, Lutschg and Meier, 1975).

NEUROPATHY IN LIVER DISEASE

Chronic Liver Disease

a. Alcoholic or Cryptogenic cirrhosis :

A number of workers have reported an association between chronic liver disease, usually alcoholic or cryptogenic cirrhosis and a mild, frequently asymptomatic, predominantly sensory neuropathy which is unrelated to alcoholism or diabetes. Kardel and Nielsen (1974) found clinical evidence of peripheral neuropathy in 68% of patients with severe chronic hepatic failure. Chari et al (1977) found clinical evidence of peripheral neuropathy in 63.3% of patients with hepatic cirrhosis and pathological

evidence of demyelination in 80% cases. Knill-Jones et al (1972) found mild peripheral neuropathy in 14 of 70 (20%) patients with chronic liver disease due to alcoholic and cryptogenic cirrhosis, haemochromatosis and chronic active hepatitis. 13 of these had clinical evidence of neuropathy and one additional patient had abnormal nerve conduction studies only.

In summary, a chronic demyelinating neuropathy, usually asymptomatic and of little clinical importance, occurs in chronic liver disease. It is difficult to determine the cause of the neuropathy. In some of the cases, it was associated with increased serum IgA and IgM, oesophageal varices, and a past history of hepatic encephalopathy (Knill Jones, 1972).

b. <u>Primary Biliary Cirrhosis</u>

Thomas and Walker (1965) described a mild sensory polyneuropathy in three female patients with primary billiary cirrhosis, resulting from xanthomatous deposits in peripheral nerves and myelinated fibre loss. Charron, Peyronnard and Marchand (1980) reported a case of a woman, aged 29 years, with primary billiary cirrhosis who presented with an asymmetrical sensory neuropathy at a time when her liver disease was minimal. The pathological changes revealed chronic axonal degeneration of a dying back type but with no lipid infiltration.

<u>Viral Hepatitis</u>

Acute polyneuritis of the Guillain Barre type is sometimes a complication of type A and type B viral

hepatitis as it is in other virus infections (Lescher, 1944; Byrne, Taylor, 1945; Lovell, 1945; Davison et al 1972; Asbury, 1975b). Usually it occurs after the onset of jaundice (Boundouresques et al, 1970, Asbury, 1976b) but may occasionally precede it (Lescher, 1944).

Chari et al (1977) reported mild clinical neuropathy mainly of a sensory type in two of 12 patients with infectious hepatitis (segmental demyelination).

Davison et al (1972) found slowing of nerve conduction velocities, followed by recovery, during episodes of severe type B hepatitis in 11 patients undergoing intermittent haemodialysis for chronic renal failure.

Farivar et al (1976) described a severe sensorimotor neuropathy that developed over a period of 4-5 weeks and persisted for over 12 months in a patient with HBs Ag positive chronic active hepatitis and cryoproteinemia. They considered that cryoprotein deposition in small blood vessels may have been responsible for the neuropathy.

NEUROPATHY IN GASTROINTESTINAL DISORDERS

Peripheral neuropathy of a predominantly sensory type is a common manifestation of pernicious anaemia. The symptoms are those of numbness and tingling in the extremities and there are signs of distal sensory loss with diminished position and vibration sense and depressed reflexes. Electrophysiological studies have demonstrated peripheral nerve involvement in 65% of patients with

untreated pernicious anaemia (Cox-Klazinga and Endtz, 1980). Subacute combined degeneration of spinal cord may be associated with peripheral neuropathy. Extensor plantar response in the presence of absent reflexes and loss of sensation should always alert the clinician to the possibility of vitamin B_{12} deficiency. Vitamin B_{12} deficiency can also result from malabsorption following total gastrectomy, carcinoma of the stomach, partial gastrectomy, small bowel resection, tropical sprue, regional ileitis, coeliac disease. Whipple's disease, scleroderma, blind loops, strictures, jejunal and ileal diverticulosis and stagnant loops due to gastrocolic and other fistulae. Cooke et al (1963) studied neuropathy in patients with jejunal diverticulasis and it was not uncommonly the presenting feature of the condition with symptoms of paraesthesiae. In vitamin B_{12} neuropathy, the serum vitamin B_{12} is usually below 80 pg per ml (normal range is from 100 to 960 pg per ml). On treatment, striking improvement is expected in the symptoms of polyneuropathy.

The neuropathy of vitamin B_1 deficiency may also be a complication of malabsorption or of persistent vomiting. Burning feet syndrome may be a complication of riboflavin, pyridoxine or pantothenic acid deficiency although the precise mechanism of the symptoms has not been adequately demonstrated (Pallis and Lewis, 1974).

The vitamin E deficiency may also occasionally be responsible for peripheral neuropathy in chronic intestinal

malabsorption. Intestinal fat malabsorption can cause deficiency of all fat soluble vitamins including Vitamin E and children with chronic cholestatic liver disease appear to be particularly susceptible, due to a combination of malabsorption of vitamin E and trapping of vitamin in plasma by the associated hyperlipoproteinemia. The manifestations of deficiency includes areflexia ~~are flexia~~, gait disturbance, decreased proprioceptive and vibratory sensations, and paresis of gaze and are associated with degeneration of the posterior columns of the spinal cord, selective loss of large caliber, myelinated axons in the peripheral nerves and appearance of spheroids in the gracile and cuneate nuclei of the brain (Harrison, 12th edition). Cerebellar ataxia may be associated with a predominantly sensory neuropathy (Harding et al, 1982). It seems likely that vitamin E deficiency causes a central peripheral distal axonopathy (Harding et al, 1982).

Tropical sprue is a malabsorptive disorder of unknown cause affecting residents of or visitors to tropical regions.

Patients are frequently deficient in iron as well as vitamin B_{12} and folate. Tropical sprue may present with paraesthesia due to peripheral neuropathy (Pallis and Lewis 1974). Iyer et al (1973) reported clinical and electrophysiological studies in patients with tropical sprue and found that peripheral neuropathy was relatively common.

Cooke and Smith (1966) described clinical and pathological findings in 16 patients with adult coeliac disease (Nontropical sprue, gluten induced enteropathy) who developed neurological complications including peripheral neuropathy, myelopathy and cerebellar degeneration. The neuropathy appeared to be of the axonal or dying back type (Cooke, Johnson and Woolf, 1966). The cause remains unknown but does not seem to be due to vitamin B_{12} or folate deficiency.

Peripheral neuropathy which improved following treatment of the infection has been described in two patients with giardiasis (Bassett, Danta and Cook, 1978).

PERIPHERAL NEUROPATHY IN PELLAGRA

Sensory symptoms consist of pain in the limbs with tender muscles and superficial anaesthesia and analgesia, often with loss of appreciation of passive movements of the toes. Visual impairment and diplopia may occur. Dysarthria and dysphagia may develop in the later stages, together with tremor and ataxia, especially in the lower limbs. The tendon jerks may be increased at first but are later lost. The plantar reflexes may be extensor, but spastic paraparesis is relatively rare (myelopathy).

Changes in peripheral nerves are less conspicuous and consist mainly of patchy demyelination.

PROTEIN CALORIE MALNUTRITION

Although protein calorie malnutrition is rampant amongst under privileged Indian children, evidence of peri-

pheral neuropathy directly related to it is not forthcoming. Sachdev, Taori and Pereira (1971) reported muscle wasting and weakness with a waddling gait, hypotonia and hyporeflexia in a high proportion of these children. No sensory disturbances was noted. Reduction in motor nerve conduction velocity, small motor units and less commonly fibrillation potentials were found. Three muscle biopsies showed small atrophic fibres in groups. They considered that this disorder was due to a motor peripheral neuropathy or anterior horn cell disease, mentioning that it may have been caused by the commonly accompanying vitamin B complex deficiency rather than protein calorie malnutrition.

Dastur et al (1977a) studying children with protein calorie malnutrition, found on quantitative histology of their sural nerve biopsy that :

1. There was a retardation or suppression of development of large myelinated fibres, the severity depending on the degree of malnutrition regardless of age.

2. There was no difference in the mean nerve fibre density, compared with controls, although there was a greater variation in the myelinated fibre density. They did not detected any peripheral neuropathy in these children nor did they suggest possibility of it occurring with sustained malnutrition alone or with additional toxic or metabolic factors.

PREGNANCY

The nutritional neuropathies may occur in pregnancy due to increased metabolic demand and/or less intake of nutrients, due to excessive vomiting, anorexia etc. The sensorimotor type is usual presentation.

The carpal tunnel syndrome may be aggravated or become symptomatic in pregnancy.

DIABETIC NEUROPATHY

Rollo (1798) was the first to suggest the involvement of the nervous system in patients with diabetes mellitus. In 1864 Marchal de Calvi postulated that diabetes could cause neuropathy and noted pain and sensory loss in patients with diabetes. In 1884, Bouchard reported the absence of reflexes in some diabetic patients and in 1885, Pavy described for the first time, with remarkable acumen and precision, the clinical features of a peripheral neuropathy associated with diabetes mellitus.

The true incidence of diabetic neuropathy in any given population is not yet established by good, reliable population studies. This is in contrast to the data available on related diseases such as coronary artery disease and hypertension. The principal weaknesses of population surveys of diabetic neuropathy are :

1. Imprecise terminology.
2. Poorly defined criteria, and
3. Skewed study populations, therefore, prevalence estimates vary widely.

CLASSIFICATION

Generally speaking, peripheral nervous system disorders of diabetes have attracted more attention than those of CNS. Many classifications of diabetic neuropathy have been proposed in the past 100 years. Some are mentioned here :

In 1888 Leyden classified three types :

1. Neuralgic, (2) Paralytic and (3) Pseudotabetic.

In 1936, Jordan proposed a classification based on his study of diabetic patients with neuropathy as follows :

1. A hyperglycaemic type with symptoms but without signs which responded to adequate treatment of diabetes.
2. A circulatory - degenerative type and
3. A neuritic type.

In 1945, Sprague cited by Treusch described as follows :

1. Diabetes with pain, in which the diabetes is out of control and symptoms improve with treatment.
2. Ischaemic neuropathy.
3. Diabetic polyneuritis.
4. Visceral neuritis.

Sullivan classified diabetic neuropathy into two categories, a symmetrical sensory and an asymmetrical motor neuropathy. Goodman et al classified diabetic neuropathy into three types :

1. Functional neuropathy in patients with uncontrolled diabetes without concommitant objective evidence of neurological involvement (similar to Jordan's hyperglycaemic neuritis).
2. Organic neuropathy characterised by objective signs.
3. Post treatment neuropathy.

In 1964, Locke proposed an anatomical classification as follows :

1. A radiculopathy, when the lesion is of nerve root and the main features are pain and sensory loss in the distribution of a dermatome.
2. A mononeuropathy, when a mixed spinal or cranial nerve is affected and clinical picture is one of pain, weakness, change in reflexes, sensory loss in the distribution of a mixed spinal or cranial nerve.
3. Polyneuropathy, when the distal portions of many nerves are affected, resulting in absent reflexes mild peripheral weakness and a typical glove and stocking sensory loss.

Classification of Diabetic neuropathies by topography :

1. Distal symmetrical polyneuropathy.

(a) Mixed sensory-motor-autonomic neuropathy.

(b) predominantly sensory neuropathy.

i) predominantly large fibre.

ii) mixed large and small fibre.

iii) predominantly small fibre.

(c) Predominantly motor neuropathy.

(d) Predominantly autonomic neuropathy.

2. Symmetrical proximal motor neuropathy.

3. Focal and multifocal neuropathies.

(a) Asymmetrical proximal motor neuropathy.

(b) Cranial neuropathy.

(c) Intercostal and other mononeuropathies.

(d) Entrapment neuropathies.

The three major neuropathic syndromes occur in diabetes, of which distal symmetrical polyneuropathy is the most common. Proximal motor neuropathy and focal neuropathies are rare in comparison. To make matters more complex, two or more forms of neuropathy often are encountered in the same diabetic patient.

Diabetic poluneuropathy has become the best understood human metabolic neuropathy. The prevalence of polyneuropathy in diabetic population has been estimated from 0-93% (Bruyn and Garland, 1970; Thomas and Eliasson,1975). A balanced view of prevalence comes from the studies of Pirart, who found evidence of neuropathy by clinical examination in about 8% of diabetics at the time of diagnosis increasing to 50% after 25 years of diabetes(Pirart,1978).

In most cases diabetic polyneuropathy involves a combination of sensory, motor and autonomic nerve fibre abnormalities. Cutaneous sensibility is reduced in a stocking and glove distribution, often associated with decreased vibratory and proprioceptive perception in the

limbs, reduced or absent ankle jerks, mild distal muscles weakness and autonomic dysfunction. These features may ge indistinguishable from those that occur in other acquired polyneuropathies.

PATHOLOGY

Diabetic polyneuropathy is best classified as an axonal neuropathy, in that the predominant neuropathic feature is nerve fibre loss (Vital and Villat, 1980; Greenbaum et al, 1964; Chopra and Hurvitz, 1969; Behse, Buchthal and Carlsen, 1977). A proximal to distal gradient of myelinated fibre abnormalities has been found at autopsy (Chopra and Fannin, 1971) and in an intramuscular twig nerve biopsy study of asymptomatic diabetic patients(Reske-Nielsen, Harmsen and Vorre, 1977). Denervation changes are evident in histologic Sections of distal muscles. When examined, the extent of fibre loss has paralleled the degree of clinical dysfunction and it appears that denervation changes are sufficient to account for the symptoms and signs in diabetic polyneuropathy. Ultrastructural studies of diabetic nerves have not demonstrated distinctive features in affected axons (Brown, Martin and Asbury, 1976; Bischoff, 1973; Vital et al, 1973). This pattern of nerve fibre damage and neurogenic atrophy is shared with most toxic and metabolic neuropathies (Asbury and Johnsen, 1978) and is not unique to diabetes.

Thomas and Lascelles (1966) and others (Chopra Hurvitz and Montgomery, 1969; Dyck et al, 1980; Bischoff,

1973; Behse, Buchthal and Carlsen, 1977) described an increased incidence of segmental demyelination in diabetic nerves. On occasion extensive demyelinative-remyelinative changes lead to frank onion bulb formation (Vital and Vallat, 1980; Ballin and Thomas, 1968). Demyelination in diabetic neuropathy cannot be explained as a secondary response to axonal atrophy (Sugimura and Dyck, 1981) and the occurrence of the segmental demyelination suggest a selective Schwann cell disorder that is independent of axonal loss (Thomas and Lascelles, 1966; Chopra, Hurwitz and Montgomery, 1969). While segmental demyelination is prominent in some cases of diabetic polyneuropathy, it may be only a minor neuropathological feature in others(Behse, Buchthal and Carlsen, 1977; Brown, Martin and Asbury, 1976).

Traditional silver staining techniques have demonstrated a decrease in unmyelinated fibre numbers in somatic and autonomic nerves of diabetics (Martin, 1953), and unmyelinated fibre loss has been confirmed by electron microscopy (Behse, Buchthal and Carlsen, 1977; Bishoff,1973; and Vital et al, 1973). In a morphometric study of two cases with painful neuropathy, increased numbers of very small unmyelinated axons (0.1-0.2 um diameter) suggested axonal regeneration with sprouting in concert with reduced unmyelinated fibres of normal caliber (0.2-2.0 um diameter) (Brown, Martin and Asbury, 1976). This probably reflects concurrent fibre degeneration and regeneration, which also occurs in other axonal polyneuropathies.

The pathology of blood vessels in diabetic peripheral nerves has been studied with interest because the other important late complications of diabetes are the microvascular disorders. Endoneurial capillaries are thickened (Fagerberg, 1959; Vital and Vallat, 1980; Behse, Buchthal and Carlsen, 1977) and perineurial basement membranes are widened (Johnson, Brendel and Meezan, 1981). A permeability disorder at the blood nerve or blood-perineurial barrier in diabetics could lead to endoneurial metabolic derangements, possibly resulting in neuropathy. However, vascular abnormalities and neuropathy could occur independently as a consequence of long standing diabetes, and their association does not indicate a causal relationship. Small vessel occlusion has been described in diabetic nerves (Timperley et al, 1976; Williams et al, 1980) and Sugimura and Dyck (1982) found focal areas of myelinated fibre loss in proximal nerves of two autopsied patients with polyneuropathy, in a pattern similar to that seen distal to experimental nerve infarcts (Parry and Brown, 1982). This raises the intriguing possibility that proximal occlusion microvascular disease could underlie the diffuse distal polyneuropathy that occur in diabetes.

NEUROPHYSIOLOGY

At times, nerve conduction velocities are slowed to a greater degree than would be expected by axonal loss alone, which probably reflects the consequences of segmental demyelination. These may be a very small degree of further

slowing that has not been explained on a structural basis (Behse, Buchthal and Carlsen, 1977). This poorly understood 'Metabolic' phenomenon seems to underlie the small improvement in motor conduction velocity that follows insulin or other treatment in early diabetes (Ward et al, 1971; Gregerson, 1968b; Judzewitsch et al, 1982).

A recent study, done by OP Gupta et al (1989) has shown that patient of diabetic neuropathy, 41.6% had evidence of decreased motor unit potentials and 16.6% showed spontaneous fibrillatory activity.

METABOLIC ABNORMALITIES AND IMPAIRED NERVE FUNCTION

Hyperglycemia alters nerve metabolism in several ways. Thorough competitive inhibition of sodium dependent myoinositol uptake and increased polyol (Sorbitol) pathway activity, hyperglycaemia reduces nerve myoinositol content, alters nerve phosphoinositide metabolism and impairs sodium-potassium ATPase activity. A major fraction of testing peripheral nerve utilization occurs via the Mg^{++} dependent Na^{+} and K^{+} stimulated adenosinetriphosphatase (sodium-potassium ATPase EC 3.6.1.3) (Ritchie, 1967). Normal peripheral nerve maintains a tissue to plasma myoinositol concentration gradient of 90-100 fold. This concentration is reduced in both human and animal diabetic peripheral nerves. The impairment of the electrogenic sodium-potassium ATPase secondarily and acutely slows nerve conduction velocity and inhibits other sodium gradient dependent processes such as myoinositol and aminoacid uptake and

intracellular water homeostasis. Other membrane defects occur as a consequence of altered inositol phospholipid metabolism, independent of sodium-potassium ATPase, possibly involving other membrane bound proteins such as the voltage dependent sodium channel or other membrane cationic ATPases. Elevated tissue glucose levels also result in non enzymatic glycosylation of nerve proteins, potentially impairing their function. These abnormalities become self reinforcing cyclic defects, with potentially widespread pathophysiological implications, leading to chronically slowed nerve conduction, impaired axonal transport, altered intermediary metabolism and eventually, structural damage to diabetic peripheral nerve fibres.

SEVERITY OF DIABETIC NEUROPATHY (IGCP Jan. 1992).

A recent detailed review on the staging of diabetic neuropathy suggested the following system for purposes of standardization of definitions in prospective multicentre clinical studies and in clinical practice.

- Stage 0 (no neuropathy) - no symptoms and fewer than two abnormalities of testing including autonomic function.
- Stage 1 (Asymptomatic neuropathy) - no symptoms but two or more abnormalities of functional testing.
- Stage 2 (Symptomatic neuropathy) - symptoms of a lesser degree along with two or more functional abnormalities.
- Stage 3 (Disabling neuropathy) - disabling symptoms and two or more functional abnormalities.

The successful use of the aforesaid staging method depends on appropriate assessment of signs and symptoms, accompanied by electrophysiological measures of pain, temperature and vibration sensations.

SENSORY POLYNEUROPATHY IN DIABETICS

It is useful to divide all abnormal sensory phenomena into two great categories, positive and negative. Positive phenomena includes tingling, pins and needles, pricking, bandlike sensations, lightening like shooting feelings(Lancinations), aching and knifelike, twisting, drawing, pulling, tightening, burning, searing, electrical and raw sensations. These are the actual words, used frequently by patients. These sensations may or may not be experienced as painful. It is thought that the pathophysiological basis of positive phenomena resides in the ectopic generation of volleys of impulses at some site of lowered neural threshold along the sensory pathways, either in peripheral or central sensory fibres, such trains of ectopically generated afferent impulses arising from sites other than normal peripheral nerve receptors determine the quality of the abnormal sensations experienced, depending upon the number, rate and distribution of impulses and the type and function of nerve fibres, in which they arise.

Positive phenomena represent heightened activity in sensory pathways, therefore they are not necessarily associated with any demonstrable sensory deficit upon examination.

Negative phenomena result from loss of sensory function and are characterized by numbness or diminution or absence of feeling in a particular distribution. Negative phenomena, in contrast to positive phenomena, are accompanied by abnormal findings on sensory examination.

In disorders affecting peripheral sensations, it is estimated that at least one half of afferent fibres innervating a given site, must be lost or functionless in order for sensory deficit to be demonstrated. This estimate probably varies according to how rapidly sensory fibres have lost function. If the rate of loss is slow and chronic, lack of cutaneous feeling may be unnoticed by the patient and difficult to demonstrate on examination, even though few sensory fibres are functioning. Rapidly evolving sensory abnormality usually evokes positive phenomena of some type and is more readily recognised by patients than insidious deafferentiation. Subclinical degrees of sensory dysfunction not demonstrable on clinical sensory examination may be revealed by sensory nerve conduction studies or somatosensory cerebral evoked potentials.

Both large and small fibre modalities may be involved in diabetics. Sensory abnormalities may range from mild toe numbness to profound anaesthesia with neuropathic ulcers and arthropathy. Sensory deficit occur in a symmetrical stocking-glove pattern, a feature that is easily overlooked if the level of hypoesthesia reaches proximally than the groin and shoulders. At that point the presence of a coexisting vertical anterior chest band of hypoesthesia will be demonstrable (Sabin, Geschwind and Waxman, 1978).

confirming the fibre length dependent nature of this polyneuropathy.

In one group of patients, there is a disproportionate loss of large fibre functions, manifested by impaired balance, decreased perception of distal vibration and position sense and loss of ankle jerks. In its most severe form position sense loss may result in sensory ataxia, the pseudotabetic form of diabetic neuropathy. Further, confusion with tabes dorsalis may arise if the pupils are small and sluggishly reacting to light, as occurs in elderly diabetics (Smith et al, 1978).

In another group of patients, small fibre modalities are most affected. Pain and temperature sensibility are disturbed with relative preservation of position and vibration sense and reflexes are normal or nearly so. (Brown, Martin and Asbury, 1976). Disabling spontaneous pains, dysesthesias and paraesthesias are common associated features. Orthostatic hypotension and sexual dysfunction seem to be especially common in this group, reflecting the coexisting autonomic neuropathy.

Several kinds of pains may be associated with diabetic sensory neuropathy e.g. :

- Typical neuropathic distal paraesthesias (spontaneously occurring uncomfortable sensations) or dysaesthesias (contact paraesthesias).
- Excessive skin hypersensitivity to light touch, reminiscent of reflex sympathetic dystrophy(Causalgia).

- Shooting or stabbing pains, which are multifocal in location and arresting in their impact.
- Superficial cutaneous burning pain.
- Bone-deep, aching, tearing pain, present throughout the day, although with varying intensity.
- Cramps in the small muscles of feet, later ascending to calves or thighs.
- Diabetic thoracic radiculopathy (Kikta, Breuer, Wilbourn 1982) - severe chest or abdominal pain with associated dysaesthesia and sensory loss corresponding to inter-costal nerve distribution, but often unilateral and associated with EMG evidence of denervation.
- Acute painful neuropathy, developing in males, after severe weight loss, causing continuous burning lower limb pain and dysaesthesiae with little sensory loss, preserved reflexes, no motor weakness but with impotence and depression, recovering in a few months with good control of diabetes and weight gain (Archer et al, 1983).

The paradoxical coexistence of spontaneous pain and insensitivity to painful stimuli in neuropathic individuals has not been explained fully. It seems more likely that pain results from increased activity of injured small diameter fibres (Brown, Martin, Asbury, 1976; Dyck, Lambert, O'Brien, 1976). Regenerating nerve fibres in experimental neuromas fire at abnormally low thresholds

and with rapid rates (Wall and Gutnick, 1974) and depolarization of damaged or regenerating fibres in humans with neuropathy could contribute to the pain in these patients.

Much less common is diabetic truncal neuropathy, often giving a band or girdle like area of sensory loss on the anterior trunk around the chest wall in the distribution of thoracic intercostal nerves. This is usually seen in patients with severe associated distal neuropathy in the limbs as well as autonomic neuropathy (Sabin, Geschwind and Waxman, 1978).

MOTOR NEUROPATHY IN DIABETES

Loss of tendon reflexes and of vibration sense in lower limbs is very common in diabetes in the absence of other clinical signs of neuropathy and in such cases nerve conduction is usually slowed.

Diabetic amyotrophy, characterised by pain, tenderness and weakness of muscles, usually limited to anterior aspect of one or both thighs, is often due to a unilateral or bilateral femoral nerve neuropathy, but is not due to mononeuritis multiplex as there is generally evidence of a subclinical generalised neuropathy (William and Mayer, 1976) and the condition seems to be metabolic rather than vascular (Chakravorty et al, 1977).

Diabetic proximal motor neuropathy may be symmetrical or asymmetrical. Clinical and EMG findings could be explained by dysfunction of anterior horn cells,

motor roots, the lumbosacral plexus or intramuscular nerve twings (Chokroverty et al, 1977). Satisfactory functional recovery occurs in most cases (Garland, 1955; Casey and Harrison, 1972), often shortly after institution of insulin therapy (Hamilton, Dobson and Marshall, 1968).

Ocular mononeuropathies are sufficiently common in diabetes that their occurrence in isolation should suggest the diagnosis. Oculomotor neuropathy is most often encountered, manifested by painful ophthalmoplegia of sudden onset, with pupillary sparing (the preservation of circumferentially located parasympathetic fibres). The basis of this mononeuropathy appears to be centrofascicular ischemia of the oculomotor nerve. Acute trochlear, abducens and facial nerve palsies are thought to occur with increased frequency in diabetes and presumably have the same acute ischaemic basis. Prognosis for recovery is good. If the neuropathy does not improve within 3-6 month or if more than one nerve is affected, another etiology should be sought.

Entrapment mononeuropathies, single or multiple either clinically evident or demonstrable only electrophysiologically are frequently associated with diabetic polyneuropathy(Mulder et al, 1961; Gilliatt and Willison,1962). In one unpublishedseries of 38 patients, Asbury found clinical or electrophysiological evidence of entrapment neuropathy in 40% of all individuals examined. Diabetic entrapment neuropathies occur at common sites of nerve compression,

including the wrist and palm (median nerve) the elbow (ulnar nerve) and the fibular head (Peroneal nerve).

AUTONOMIC DYSFUNCTION IN DIABETES

It is of clinical and prognostic importance to assess autonomic damage in peripheral nerve disease particularly in patients with diabetes mellitus. Diabetics with autonomic neuropathy may have an increased incidence of cardiac arrest and sudden death (Page and Wattkins, 1978; Clark Ewing and Campbell, 1979). Autonomic dysfunction is often present in diabetic individuals without autonomic symptoms (Pfeifer et al, 1982).

A. Cardiovascular manifestations :

- Resting bradycardia or tachycardia.
- Orthostatic hypotension and frank syncope or dizziness.
- Loss of heart rate variation during deep breathing (sinus arrhythmia).
- Cardiorespiratory arrest and sudden death.

B. Gastrointestinal tract Manifestations :

- Difficulty in swallowing.
- Delayed gastric emptying.
- Constipation or diarrhoea(often nocturnal).

C. Sexual dysfunction :

- Impotence and retrograde ejaculation.
- Premature ejaculation.

Diabetic autonomic neuropathy of the pelvic parasympathetic nerves (nervi erigentes) accounts for about 60% of impotence in diabetic males and diabetic men tend to become impotent at an earlier age than others. Vasculopathy may be additional factor for sexual dysfunction in males. Careful studies indicate that diabetes has no effect on sexual performance in women. Perhaps, it is a psychological aspect of sexual behaviour that accounts for the remarkable differences in the effect of autonomic neuropathy in the two sexes (Ellenberg, 1980b).

D. <u>Bladder Dysfunction</u> :

Inappropriate contractions or failure of external or internal urethral sphincter relaxation, simultaneous with detrusor contraction, result in dysfunction termed detrusor-urethral sphincter dyssynergia, a feature of diabetic peripheral neuropathy. Neurogenic bladder involvement in diabetics (Diabetic cystopathy) begins insidiously and symptoms usually appear when the disease is advanced. Diabetic cystopathy and peripheral neuropathy occur together in 75-100% of patients and some consider the presence of peripheral neuropathy a sine qua non for the diagnosis of diabetic cystopathy. On the other hand, in those who have peripheral nerve dysfunction, 83% have diabetic cystopathy on cystometric examination. The absence of desire to void when the bladder contains over 500 ml and increased bladder capacity are indications of diabetic cystopathy.

Ch Characteristically, the patient with a diabetic neurogenic bladder has residual urine, infection, pyelonephritis, sepsis, and azotemia. He may present with the complaints of increasing intervals between voiding and urination may occur once or twice a day only. This is often accompanied by the need for straining to initiate and maintain voiding, weakness of the stream, dirbbling and a sensation of incomplete emptying. Urethral orifices are often incompetent showing reflux during radiographic studies.

E. Sweating Abnormalities

Diabetic anhidrosis is a condition in which sweating is absent in the lower limbs or trunk of patients with diabetic neuropathy (Goodman, 1966). Patients with this disorder are intolerant to heat, but may experience excessive perspiration on the head, face, and neck or compensatory hyperhidrosis that is particularly profuse on the face at meal time (Enough tobe socially unacceptable). Gustatory sweating in patients with diabetic neuropathy is usually confined to the territory of superior cervical ganglion. Gustatory sweating is attributed to sprouting or cross innervation of fibres and suggests that in diabetic autonomic neuropathy, despite the persistence of the metabolic abnormality presumably responsible for autonomic disturbances, regeneration of axons is possible(Watkins, 1973). All patients with diabetic anhidrosis or hyper-

hidrosis of face have abnormal autonomic function in other systems and organs.

Singh and Singh et al (1987) using indirect immunofluorescent technique, studied the antivagal and antisympathetic antibodies in case of diabetes mellitus with and without autonomic neuropathy to explore the possibility of autoimmunity being basis of diabetic autonomic neuropathy. Antivagal antibodies were present in 20% cases of diabetes mellitus with autonomic neuropathy It was not detected in even a single case of diabetes mellitus without autonomic neuropathy as well as in any control case. It signifies its highly specific nature and suggests that autonomic neuropathy in diabetics could be autoimmune in nature. However, study of antisympathetic antibodies suggests its non specific nature and needs further exploration.

F. Dysfunction of Pupils

Human pupils react continuously to changes in lighting due to a balance between sympathetic and parasympathetic innervation of the iris. Parasympathetic denervation supersensitivity results in pupillary constriction with the instillation of 2.5% methacholine, which in the normal pupil, does not cause constriction. The instillation of 1 : 1000 epinephrine into the conjunctival sac of a normally innervated iris will not cause pupillary dilatation, but will do so only in presence of sympathetic denervation.

Parasympathetic denervation supersensitivity occurs in 81% of patients with diabetic autonomic neuropathy(Sigsbee et al, 1974). A finding most prevalent in patients who had been diabetic for at least 2 years.

NEUROPATHY IN MYXOEDEMA AND PITUITARY DISORDERS

In myxoedema followings are described :

- Carpal tunnel syndrome (Murray and Simpson, 1958).
- Symmetrical predominantly sensory neuropathy. (Nickel et al, 1961).
- Diffuse demyelinating sensorimotor neuropathy (Dyck and Lambert, 1970).
- The muscle percussion is not associated with a recordable electrical discharge.
- Loss or delayed response of tendon reflexes.

In acromegaly followings are described :

- Carpal tunnel syndrome.
- Polyneuropathy (Low, Mcleaod et al, 1974).

NEUROPATHY IN PORPHYRIA

- Peripheral neuropathy accompanies the hepatic porphyrias.
- Acute attacks are precipitated by fasting, infections, usual therapeutic doses of barbiturates, anticonvulsants, estrogens, contraceptives and alcohol and may lost from days to months and vary in frequency and severity.
- Peripheral neuropathy is predominantly motor but pain in the limbs and back may precede the weakness. The upper limbs may be more severely affected than the lower

and proximal muscles may be more severely affected than distal. Paraplegia or complete flaccid quadriplegia may ensue. Cranial nerve involvement may lead to optic nerve atrophy, ophthalmoplegia and dysphagia. Deep tendon reflexes are diminished or absent.

- Autonomic manifestations may be present.
  - Tachycardia, hypertension, postural hypotension.
  - Abdominal pain, severe vomiting, constipation.
  - Urinary retention, excessive sweating, hyponatremia, hypomagnessemia.
- Although the neuropathy is reversible to a surprising degree, residual paresis may lost for years following an acute attack.

NEUROPATHY IN MALIGNANCIES

In the evaluation of a possibly paracarcinomatous neuropathy, it is particularly helpful to ascertain whether the neuropathy (1) affects motor fibres, sensory fibres or both (2) predominantly involves axon or myelin or (3) occurs with an abnormal serum paraprotein. The following patterns are recognised :

1. Acute inflammatory demyelinating polyneuritis (AIDP, Guillain-Barre) - AIDP may be associated with Hodgekin's disease.
2. Chronic inflammatory demyelinating polyneuropathy (CIDP).

It is characterised by chronic progressive or relapsing course, more prominent involvement of sensory nerves, lack of involvement of autonomic nerves, responsiveness to immunotherapy and in many cases, by the presence of a serum paraprotein, typically a monoclonal immunoglobulin (M Component).

The two subtypes of CIDP are recognised :

A. IgM anti MAG neuropathy - It is more sensory than motor. It is associated with a monoclonal IgM, that reacts with a myelin associated glycoprotein (MAG) in peripheral nerve myelin. This pattern of reactivity occur in about half of patients with an IgM gammopathy and neuropathy.

B. It occurs with osteosclerotic myeloma and monoclonal IgG or IgA antibodies that do not react with MAG. This type is predominantly motor and often quite indolent although it may eventually produce severe limb wasting. Sensory and autonomic features are unusual.

CIDP occurs in association with solid tumours of lung, breast, stomach, Waldenstrom's macroglobulinemia, gamma heavy chain disease, Lymphoma.

3. Subacute sensory Neuronopathy : It is a ganglioradiculitis, clinically heralded by the subacute appearance of paraesthesias and pain in distal limbs and truncal sensory ataxia. Although initially restricted only to arms or legs, the symptoms eventually affect all four limbs. In many cases the underlying malignancy

is oat cell cancer of lung.

4. Sensorimotor neuropathy : This is the most common type of paraneoplastic neuropathy, has been reported with several types of tumours (lung oat cell, breast stomach) and hematologic malignancies (Hodgekin's disease, lymphoma, multiple myeloma), insulinoma, Infrequently, these neuropathies remit spontaneously, often they progress even with aggressive treatment of underlying malignancy.

5. Subacute motor neuronopathy : This causes slowly progressive weakness in patients with lymphoma or myeloma.

Peripheral neuropathy in leukaemia is most commonly the result of infiltration, haemorrhage and infarction in the peripheral nerves (Mcleod and Walsh, 1975a; Henson and Urich, 1982). Peripheral neuropathy is rare in acute leukaemia. It is more common in chronic lymphatic leukaemia in which there may be an associated acute polyneuritis of the Guillain-Barre type or a chronic sensorimotor neuropathy. Peripheral neuropathy is an unusual complication of chronic myeloid leukaemia (McLeod and Walsh, 1975a; Henson and Urich, 1982).

INFECTIVE CONDITIONS

Leprosy

Fite (1943) stated that all leprosy is neural leprosy" the difference is only in the degree and type

of infection of the peripheral nervous system which extends from the dermal branches to the posterior root and sympathetic ganglia. Antia (1974) sums up the evidence for this succinctly, mentioning that biopsy from even the first small skin patch shows involvement of the cutaneous nerves as the earliest histological evidence of leprosy.

The characteristic lesion is a granuloma the leprous nodule, composed of large connective tissue cells, the lepra cells containing lepra bacilli and surrounded by epitheliod and plasma cells and fibroblasts. In tuberculoid, neuritis, which can occur without skin lesions (Jopling and Morgan-Hughes, 1965), the powerful immune responses of the host, represented by focal masses of epitheliod cells in the lesions keep the bacilli in abeyance but the entire nerve parenchyma undergoes damage at sites of predilection, so that there is extensive Wallerian degeneration distal to these lesions (Dastur and Kabholker 1974). In lepromatous neuritis, on the other hand, the immune response is suppressed, bacilli are present in large numbers, especially in Schwann cells, there are usually extensive associated [illegible] lesions and there is more diffuse damage in both peripheral nerve myelin and axons (Dastur, 1967). There is marked activation of phagolysosomes (Dastur and Porwal, 1979). The dorsal root ganglia, the trigeminal ganglia and the anterior horns of spinal cord may be invaded and within the cord, fibres derived from the dorsal root ganglia degenerate. There is often

associated lepromatous myositis (Sebille and Gray, 1979).

The onset of symptoms is gradual. Prodromal toxaemic symptoms may occur and are followed by limb pains, referred to the distribution of the peripheral nerves and often a sense of numbness of the extremities. Symptoms tend to be symmetrical, anaesthesia of the glove and stocking distribution developing, together with atrophic paralysis of peripheral limb muscles. Pure neural tuberculoid leprosy without skin lesions is uncommon. In advanced lepromatous leprosy, there may be bizarre patterns of sensery impairment in the skin of upper limbs,,with comparative sparing of sensation in the palms and antecubital fossae but dense sensory loss on the dorsum of hands and forearms, this seems to be due to the fact that the fine cutaneous nerve endings are most extensively damaged in cooler skin areas (Sabin, 1969). The facial anaesthesia and paralysis due to involvement of the fifth and seventh cranial nerves are common (Antia et al, 1966). Trophic changes are conspicuous in the limbs. Bullae, ulceration and necrosis of the phalanges occur and the digits may ultimately destroyed. Thickening of the peripheral nerves is usually, but not invariably, palpable. The conduction velocity is slowed and EMG indicates denervation (Sebille and Gray, 1979).

Saxena et al (1990) reported a patient with leprosy who had an unusual combination of multiple cranial nerve involvement (left ophthalmic and maxillary division

of fifth nerve, left seventh nerve, left auditory nerve) and presented with trigeminal neuralgia.

Dastur (1976) mentioned that borderline tuberculoid variety predominates in India and the nonlepromatous types considered together constitute about 80% of the leprosy cases.

MALARIA

Optic neuritis and retinal haemorrhages are often seen and complete external ophthalmoplegia may occur. PZ Wadia (1990) has reported two patients with falciparum malaria, presenting with retrobulbar neuritis and improving with quinine therapy.

Chronic nervous symptoms in malaria are probably toxic in origin and are usually due to neuropathy. Trigeminal neuralgia, facial palsy, mononeuropathy and polyneuropathy may all occur.

TYPHOID

Polyneuritis is a rare sequel, predominantly involving the feet and causing tenderness of the soles. Similar complications may occur in paratyphoid fever, but much less frequently than in typhoid.

TYPHUS FEVER

The cranial and peripheral nerves frequently suffer. Optic neuritis may occur. Facial paralysis is particularly common and deafness may develop. In the peripheral nerves the symptoms may be those of a focal

mononeuritis, associated with pain and tenderness or of a polyneuritis.

GUILLAIN BARRE SYNDROME

Acute Postinfective Polyradiculoneuropathy

It is an acute and diffuse post infective disorder of the nervous system involving the spinal roots and peripheral nerves and occasionally the cranial nerves.

Associations with infectious mononucleosis, subclinical Epstein Barr virus infection, measles, cytomegalovirus, mumps, mycoplasma, water pollution, herpes virus, immune complex nephritis, surgical operations, Hodgekin's disease, SLE, malignancy etc. have been described. The current view is that it is an inflammatory disorder due to disordered immunity, perhaps as a result of a variety of unidenfified allergens, but the possibility still exists that some cases could be due to the direct invasion of peripheral nerves by one or more viruses. There is possible association with the HLA-A_1, B_8 DRW_3 and DW haplotypes. The evidence supporting the major importance of autoantibodies and of immune complexes in pathogenesis continues to increase (Cook and Dowling, 1981).

The clinical features of GBS typically include areflexic motor paralysis with mild sensory disturbances coupled with an acellular rise of total protein in the cerebrospinal fluid by the end of the first week of

symptoms. The paralysis may affect all four limbs simultaneously or may begin in the lower limbs and spread to the upper. All the muscles of a limb are usually affected, those of the proximal segments suffering as much as, or even more severely than, those of distal segments. Occasionally weakness is even limited to proximal muscles and may be asymmetrical. In severe cases, the muscles of the neck and trunk are also involved and there is often paralysis of the facial muscles on both sides, though this is occasionally unilateral (Kimura, 1971). Dysphagia may occur as a result of pharyngeal paralysis but the palate usually escapes. Respiratory muscle involvement requires assisted respiration. The paralysed muscles are flaccid but severe wasting is exceptional. Superficial and deep reflexes are usually diminished or lost, but are rarely retained in spite of weakness of voluntary movement in the muscles concerned. The sensory symptoms are usually but not invariably present and in the early stages the patient may complain of pain, numbness and tingling in the limbs. Bilateral optic neuritis, leading to visual impairment is rare but papilloedema is seen occasionally and is usually attributed to the greatly increased protein content of the CSF with impaired absorption (Reid and Draper, 1980). General symptoms of toxaemia may be present. Cerebral symptoms are usually absent and consciousness is usually unclouded throughout but a confusional stage or even coma may rarely develop.

Autonomic manifestations include arterial hypertension, postural hypotension, localised anhidrosis, impaired baroreflex sensitivity, hyponatremia (may be due to an abnormally low resetting of osmoreceptor responses), ileus, bladder dysfunction (particularly retention), idioventricular arrhythmia (Pace, 1976), fixed tachycardia, sudden shock with loss of cardiac filling pressure. Interesting and dramatic parasympathetic discharges may occur with flushing, chest tightness and profuse bronchorrhoea.

GBS variant illnesses are well known, the most striking being the polyneuropathy with ophthalmoplegia and ataxia, described by Miller Fisher (1956). Others include descending paralysis with ocular, facial and pharyngeal paresis occurring before limb paresis, which simulates botulism or early diphtheria, instances of early and almost purely respiratory failure; pure pandysautonomic illness, described by Young et al (1975); polyneuritis cranialis and locked in coma (Carroll and Mastaglia, 1979).

Evidence of antibodies to nerve antigens or demyelinating serum factors has provided a rationale for the use of plasma exchange in its treatment.

<u>NEUROPATHY IN CONNECTIVE TISSUE AND ALLIED DISORDERS</u>

Involvement of the peripheral nervous system including the cranial nerves, is frequently seen in connective tissue disorders and may be the first clinical

manifestation in some of these diseases. Peripheral nerve disease may be primary or secondary to involvement of other organ systems (Uremic or entrapment neuropathøies) or as a result of therapy (Gold neuropathy). Primary involvement of the PNS may be in a pattern of mononeuropathy(mononeuritis including cranial nerves) or mononeuropathy multiplex(mononeuritis including cranial nerves), diffuse polyneuropathy (usually mixed sensory - motor neuropathy) or rarely, demyelinating neuropathy of Guillain Barre type.

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Although involvement of the CNS in patients with SLE is the most common and widely appreciated neurologic manifestation, peripheral nerve and cranial nerve involvement are well recognized, occurring in about 10% of patients (Berry and Hodges, 1965; Dobois, 1966; Johnson and Richardson, 1968; Feinglass et al, 1976). The pattern of PNS involvement seen are :

1. Symmetric distal sensory - motor neuropathy.
2. Mononeuropathy (mononeuritis) multiplex.
3. Cranial nerve involvement , and
4. Guillain Barre Syndrome.

Involvement of CNS may make it difficult to establish the concomittant presence of a neuropathy or to distinguish PNS from CNS localization of cranial nerve deficits (Johnson and Richardson, 1968).

1. SENSORY-MOTOR NEUROPATHY

The most common PNS involvement in patients with SLE is a symmetric subacute or chronically progressive, symmetric mixed sensory-motor neuropathy with sensory findings predominantly (Johnson and Richardson, 1968; Feinglass et al, 1976).

In addition to loss of myelinated fibres and evidence of loss of axon cylinders, pathologic studies in patients with this type of neuropathy have demonstrated varying degrees of perivascular mononuclear and polymorphonuclear cell infiltration (Lewis, 1965) and changes in blood vessels ranging from frank vasculitis with inflammatory cells (Bailey, Sayre and Clarke, 1956) to vascular changes without inflammation (Hepinstall and Sowry, 1952; Goldberg and Chitanondh, 1959) to normal vessels (XJohnson and Richardson, 1968). In other cases fibrinoid material, apparently similar to hematoxylin bodies is found and is thought to compress nerve fibres (Scheinberg, 1956). It has been suggested that such material can cause disease by mechanical effects on nerve fibres.

2. MONONEUROPATHY

Patients with SLE may present with the clinical picture of acute or subacute mononeuropathy, mononeuropathy multiplex or plexopathy (Scheinberg, 1956; Feinglass et al, 1976; Błock et al, 1979). Involvement of adjacent major nerves may result in what may appear at first to be a

distal symmetric polyneuropathy. Because of the pattern of involvement (Single large nerve in an acute or sub-acute pattern) and the presence of arteritis in some patients, it has been thought that the deposition of immune complexes is responsible for this form of neuropathy in SLE as well as in other connective tissue disorders.

3. CRANIAL NERVES

Clinical involvement of one or more cranial nerves is seen in patients with SLE, frequently in association with signs of other peripheral neuropathies or unequivocal CNS disease (Johnson and Richardson, 1968; Ashworth and Tait, 1971; Lundberg and Werner, 1972; Feinglass et al, 1976). In other patients, weakness of muscles, innervated by the cranial nerves may represent simultaneous myasthenia gravis and SLE (Denny and Rose, 1961; Wolf and Barrows, 1966).

4. GUILLAIN BARRE SYNDROME

Fairly typical instances of Guillain Barre Syndrome have been reported in patients with SLE (Clarke and Bailey, 1956; Feinglass et al, 1976), although in many the course of disease is more subacute and resembles the chronic progressive or recurrent demyelinative polyneuropathies (CRDP) (Goldberg and Chitanonth, 1959; Lewis, 1965; Johnson and Richardson, 1968). In others, the picture merges with that of a rapidly progressive distal sensory motor neuropathy in which the motor findings predominate.

Although idiopathic Guillain Barre Syndrome is clearly demyelinative, there are several features of importance to this discussion.

a. Circulating immune complexes are found in serum of patients with Guillain Barre Syndrome(Tachovsky et al, 1976; Cook and Dowling, 1981).

b. While the clinical picture in Guillain Barre Syndrome is bilateral and basically symmetric, the pathology (Asbury, Arnason and Adams, 1969) and the detailed electrophysiology (Brown, Feasby and Yates, 1981) reveals a multifocal segmental disorder.

c. It is possible that non Ig serum factors such as activated complement could cause demyelination or abnormalities in Schwann cells leading to demyelination (Lisak, Brown and Sumner, 1983).

One could then argue that if multifocal demyelination can lead to the clinically symmetric pattern seen in Guillain-Barre Syndrome of the chronic and relapsing neuropathies (Lewis and Sumner, 1982), then multiple vascular lesions within the same nerve could result in a Guillain-Barre syndrome like picture in SLE. By extension, one could postulate that many or even all neuropathies in SLE patients (and other connective tissue disorders) are vascular in pathogenesis and the clinical and pathological picture seen (diffuse polyneuropathy, typical or atypical Guillain Barre Syndrome, mononeuropathy or plexopathy) is

simply the result of the rate and pattern of lesions. Experimental acute ischaemia or infarction does not result in classic PNS demyelination but subacute or chronic ischaemia might (a) cause demyelination or (b) cause proximal lesions which distally appear diffuse (Parry and Brown, 1981).

PERIPHERAL NEUROPATHY IN RHEUMATOID ARTHRITIS

Peripheral neuropathy occurs in 1-10% of patients with rheumatoid arthritis (Johnson et al, 1959; Conn and Dyck, 1975). Several clinical patterns are seen including:

1. Entrapment neuropathies.
2. A relatively mild distal symmetric neuropathy with predominantly, if not exclusively , sensory involvement.
3. Mononeuritis or mononeuritis multiplex.
4. A severe distal sensori-motor neuropathy which is probably a result from a series of fulminant mono-neuropathies. Autonomic dysfunction may also occur (Edmonds et al, 1979).

ENTRAPMENT NEUROPATHIES

Rheumatoid arthritis patients may have any of several entrapment neuropathies(Nakano, 1978) including:

1. Median nerve in the carpal tunnel.
2. Digital branches of median or ulnar nerves.
3. Anterior interosseous nerve.
4. Ulnar nerve in Guyton's canal at the wrist or at elbow.
5. Posterior interosseous nerve syndrome at the elbow.

6. Lower sciatic nerve (with a Baker's cyst in the popliteal fossa affecting posterior tibial, peroneal or both branches of sciatic nerve).

7. Tarsal tunnel syndrome, entrapping the posterior tibial nerve in the flexor retinaculum along the medial malleolus of the ankle.

DISTAL SYMMETRIC POLYNEUROPATHY

Patients may have gradual onset with paraesthesiae and decreased sensations in lower or upper extremities or both (Pallis and Scott, 1965). Motor symptoms are frequently not present or may be impossible to discern because of deformities (Conn and Dyck, 1975). This type of neuropathy may be slowly progressive, may stabilise or occasionally progress to an extent to cause severe disability. In one patient segmental demyelination and occasional degeneration of large myelinated fibres were said to be present (Peyronnard et al, 1982). Similar findings have also been described in patients with RA without clinical neuropathy (Backett Dinn, 1972). Another patient showed intimal proliferation and Wallerian degeneration with severe loss of myelinated fibres (Beckett and Dinn, 1972), while mild ischaemia has been invoked as a possible mechanism in this syndrome, the vessels within the nerves have not always been abnormal at the level examined (Conn and Dyck, 1975) or when abnormal are often quite mild.

MONONEURITIS

Mononeuritis or mononeuritis multiplex is a well recognised complication of RA. The clinical picture evolves into a severe distal sensory-motor neuropathy. Interestingly, cranial nerve mononeuritis which is seen in SLE, MCTD, scleroderma and primary Sjogren's syndrome is rare in RA.

SEVERE DISTAL SENSORY MOTOR NEUROPATHY

This evolves rapidly and probably represents a series of mononeuritis multiplexes involving multiple nerves giving a symmetric distal picture. This type of neuropathy and mono-neuritis multiplex are most frequently seen in patients with long standing highly expressed RA, exhibiting other signs of vasculitis including rheumatoid nodules, skin vasculitis, weight loss, fever, high titre rheumatoid factor and frequently decreased serum complement (Cohn and Dyck, 1975).

Analysis of the nerves reveals segmental demyelination (Beckett and Dinn, 1972). With severe deficit, Wallerian degeneration is usually seen, especially in association with extensive vasculitis. True infarction (circumscribed necrosis of all elements) is unusual (Conn and Dyck, 1975). The lesions of ischaemia and fibre degeneration tend to be maximal in the mid arm and thigh and in cross section are seen in a central fascicular pattern(Dyck, Conn and Okazaki, 1972). This suggest that

poor collateral flow in a water shed area tends to result in greater ischaemia (Sladky, Greenberg and Brown, 1983).

MATERIAL AND METHODS

MATERIAL AND METHODS

The study was conducted in the department of Medicine, M.L.B. Medical College, Hospital, Jhansi. The cases for the study were selcted from the patients attending M.L.B. Medical College, Hospital, Jhansi with features of peripheral neuropathy or with diseases, known to cause peripheral neuropathy. In the latter category, the patients with diabetes, leprosy, diarrhoea, endocrinal disorders, taking neurotoxic drugs, collagen diseases, liver disease were considered specially for the study. A routine testing for impairment of neuropathic peripheral sensations and jerks was carried out and in other cases also to unravel any case of asymptomatic peripheral neuropathy in other diseases.

Bed side assessment of autonomic function was done in patients having features suggestive of autonomic dysfunction. The following tests were used :

1. ORTHOSTATIC CHANGE IN PULSE RATE

Pulse rate was counted first in the supine position and then in the standing position. A rise of less than 10 beats per minutes on rising was considered abnormal. (Nies, 1972; and Ewing et al, 1978 & 1981).

2. ORTHOSTATIC CHANGE IN BLOOD PRESSURE

Blood pressure in the right arm was recorded first with the patient supine and again after the patient

had been standing for 10 minutes.

Orthostatic hypotension was considered to be present if there was a fall in blood pressure of at least 30/20 mm Hg with or without giddiness or syncope. (Schata et al, 1963).

The number of investigations to be performed were decided in individual case, depending upon the clinical presentation and possible aetiological factors viz. TLC, DLC, Hb, ESR and GBP.

- Blood sugar - fasting and post prandial.
- Blood urea, serum creatinine (in suspected patients of renal insufficiency).
- Serum cholesterol,
- VDRL.
- Widal test (in patients of pyrexia of more than one week).
- Skin biopsy (in suspected leprosy patients).
- Rheumatoid factor, LE cell phenomenon in relevant cases.
- Urine - Routine and microscopic examination.
- C.S.F.
- Liver function tests.
- Nerve biopsy etc.

O B S E R V A T I O N S

OBSERVATIONS

Present work was undertaken to study patients presenting with features of peripheral neuropathy, to find out possible aetiological factors and to detect the presence of asymptomatic peripheral neuropathy in diseases known to cause this complication viz. diabetes mellitus, leprosy, patients getting neurotoxic drugs. Study consisted of history taking and physical examination of 56 consecutive patients of peripheral neuropathy, comprising of 37 male and 19 female patients (Table 1).

TABLE 1 : Age and sex distribution of cases with peripheral neuropathy.

Sl. No.	Age group (years)	Number of patients			
		Male	Female	Total	Percentage
1.	$\leq$ 10	-	-	-	-
2.	11 - 20	4	1	5	8.93
3.	21 - 30	6	6	12	21.42
4.	31 - 40	7	5	12	21.42
5.	41 - 50	12	3	15	26.79
6.	51 - 60	6	4	10	17.86
7.	$>$ 60	2	-	2	3.58
	TOTAL	37	19	56	100.00

Maximum number of patients presenting with peripheral neuropathy were having diabetes mellitus . 24(42.85%) cases out of 56 patients of peripheral

neuropathy (Table 2). Some of patients with peripheral neuropathy had two or more diseases (associations). Five patients of peripheral neuropathy with diabetes mellitus were also suffering from tuberculosis. One patient of peripheral neuropathy with diabetes mellitus was also having Buerger's disease. Out of 7 cases of peripheral neuropathy with malignancy, one patient was also having COAD. One patient of peripheral neuropathy was having tuberculosis and rheumatoid arthritis, both. One patient of peripheral neuropathy with tuberculosis was associated with chronic alcoholism. One patient of peripheral neuropathy with cirrhosis of liver was chronic alcoholic. One patient of porphyria (AIP) presented with features of Guillain Barre Syndrome.

TABLE 2 : Different diseases (associations) causing peripheral neuropathy.

Sl. No.	Diseases (Associations)	No.of cases
1.	Diabetes mellitus	24
2.	Leprosy	7
3.	Guillain Barre Syndrome	6
4.	Tuberculosis	11
5.	Malignancy	7
6.	Cirrhosis of liver	2
7.	COAD	4
8.	Typhoid	1
9.	Hypothyroidism	1
10.	Rheumatoid arthritis	1
11.	Buerger's disease	1
12.	Chronic alcoholism	2
13.	Porphyria	1

Duration of symptoms, suggestive of peripheral neuropathy in diabetes mellitus varied from patient to patient at the time of presentation (Table 3). Out of 24 cases of peripheral neuropathy due to diabetes, two (8.33%) patients had no neuropathic symptoms at the time of presentation. In other patients of peripheral neuropathy duration of symptoms ranged from one month to 16 years.

TABLE 3 : Duration of symptoms suggestive of peripheral neuropathy in diabetics.

Sl. No.	Duration of symptoms	No. of cases
1.	$<$ 6 months	7
2.	6 months - $<$ 1 year	4
3.	1 year - $<$ 5 years	9
4.	5 years - $>$ 5 years	2
	TOTAL	22

Tingling and numbness was very common in patients of peripheral neuropathy due to diabetes mellitus (Table 4). It was found in 19 (79.1%) cases. Burning sensation was complained in 1(4.1%) case. Pain weakness and giddiness were complained in 3(12.5%), 2(8.3%) and 7(29.1%) cases respectively.

Abnormalities of deep tendon reflexes in patients of peripheral neuropathy due to diabetes mellitus were observed frequently. Deep tendon reflexes were either reduced or absent. The abnormalities of knee, ankle, biceps, triceps and supinator jerks were observed in 13 (54.1%), 20(83.3%), 9(37.5%), 14(58.3%) and 14(58.3%) cases respectively(Table 5). Nine patients of peripheral neuropathy due to diabetes mellitus were having all the jerks, abnormal in every case.

Abnormalities of sensations in patients of peripheral neuropathy due to diabetes mellitus, can be detected in significant number of cases (Table 6). Abnormality was found in the form of reduced or absent sensations, mostly in the distal parts of extremities. The position sense was impaired in 7(29.1%) cases. Appreciation of vibration was found abnormal in all cases (100%). The abnormalities of touch, pain and temperature were detected in 16 (66.6%), 13(54.1%), and 13(54.1%) cases respectively. Hyperaesthesia was observed in only 1 (4.1%) case. In five cases (20.8%) of peripheral neuropathy due to diabetes mellitus, abnormalities in position sense, vibration, touch, pain and temperature were detected in each patient. In 2(8.33%) cases of peripheral neuropathy, abnormalities in pain and temperature sensations were found but touch sensation was found normal.

Table 7 depicts the features of autonomic neuropathy in patients of peripheral neuropathy, due to diabetes mellitus. Tachycardia in supine position was observed in 4(16.6%) cases and in the standing position in 14(58.3%) cases. Orthostatic change in pulse rate was observed. A rise of less than 10 beats per minute on rising was observed in 9(37.5%) cases of peripheral neuropathy. Fall of 30/20 mm Hg of blood pressure from supine to standing was observed in 5(20.8%) cases. The complaint of giddiness on standing was found in 7(29.1%) cases of peripheral neuropathy. The sluggish reaction of pupils to light was observed in 3(12.5%) cases of peripheral neuropathy due to diabetes mellitus.

Duration of symptoms suggestive of peripheral neuropathy may vary from one and half months to 18 years, in patients of peripheral neuropathy due to leprosy at the time of presentation. One patient of peripheral neuropathy due to leprosy presented with symptoms suggestive of right sided supraorbital neuralgia for 10 years. Symptoms of tingling, numbness, pain, weakness and neuropathic ulcers were observed in 1(14.2%) case, 3(42.8%), 1(14.2%), 2(28.5%) and 3(42.8%) cases out of 7 patients of peripheral neuropathy respectively.

Abnormalities in jerks were less commonly observed as compared to sensory abnormalities (Table 5 and 6). Knee, ankle, biceps, triceps and supinator jerks were found

TABLE 4 : Different symptoms in patients of peripheral neuropathy with different diseases.

Symptoms	Diabetes mellitus (n=24)		Leprosy (n=7)		G.B.Syndrome (n=6)		Malignancy (n=7)		Tuberculosis (n=6)	
	Cases $\bar{C}$ symptom		Cases $\bar{C}$ symptom		Cases $\bar{C}$ symptom		Cases $\bar{C}$ symptom		Cases $\bar{C}$ symptom	
	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage
Tingling	19	79.1	1	14.2	-	-	1	14.2	2	33.3
Numbness	19	79.1	3	42.8	-	-	-	-	-	-
Burning	1	4.1	-	-	1	16.6	-	-	1	16.6
Pain	3	12.5	1	14.2	-	-	-	-	-	-
Weakness	2	8.3	2	28.5	6	100.00	-	-	-	-
Giddiness	7	29.2	-	-	-	-	-	-	-	-
Ulcers	-	-	3	42.8	-	-	-	-	-	-
Itching	-	-	-	-	-	-	1	14.2	-	-

TABLE 5 : Abnormalities of deep tendon reflexes in patients of peripheral neuropathy with different diseases.

Name of jerk	Diabetes mellitus (n=24) Cases with abnormal jerk		Leprosy (n=7) Cases with abnormal jerk		G.B. Syndrome (n=6) Cases with abnormal jerk		Malignancy (n=7) Cases with abnormal jerk		Tuberculosis (n=6) Cases with abnormal jerk	
	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage
Knee	13	54.1	1	14.2	6	100.0	2	28.5	2	33.3
Ankle	20	83.3	2	28.5	6	100.0	2	28.5	4	66.6
Biceps	9	37.5	-	-	6	100.0	-	-	-	-
Triceps	14	58.3	1	14.2	6	100.0	1	14.2	-	-
Supinator	14	58.3	1	14.2	6	100.0	1	14.2	1	16.6

TABLE 6 : Abnormalities of sensations in patients of peripheral neuropathy with different diseases.

Sensations	Diabetes mellitus (n=24) cases with abnormal sensation		Leprosy (n=7) cases with abnormal Sensation		G.B.Syndrome (n=6) cases with abnormal Sensation		Malignancy (n=7) cases with abnormal Sensation		Tuberculosis (n=6) cases with abnormal Sensation	
	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage
Position sense	7	29.1	1	14.2	6	100.0	-	-	1	16.6
Vibration	24	100.0	7	100.0	6	100.0	4	57.1	6	100.0
Touch	16	66.6	6	85.7	4	66.6	3	42.8	3	50.0
Pain	13	54.1	6	85.7	2	33.3	2	28.5	2	33.3
Temperature	13	54.1	6	85.7	2	33.3	2	28.5	2	33.3

TABLE 7 : Evidences of autonomic dysfunction in patients of peripheral neuropathy due to diabetes mellitus.

Sl. No.	Case No.	Pulse rate			Blood Pressure (mm Hg)			Symptoms of giddiness on standing
		Supine	Standing	Difference	Supine	Standing	Difference	
1.	1	96	112	16	180/110	156/82	24/28	
2.	2	84	90	6	120/100	120/100	-	
3.	3	78	82	4	110/82	108/82	-	
4.	12	110	122	12	130/88	112/90	18/-	
5.	15	94	108	14	118/72	94/70	24/2	
6.	16	88	94	6	102/72	100/72	2/-	
7.	17	90	112	22	192/112	130/92	52/20	
8.	18	96	122	26	110/62	82/60	28/2	+
9.	23	74	80	6	134/100	98/74	36/26	+
10.	24	84	90	6	116/80	118/80	-	
11.	25	86	88	2	128/82	110/78	18/4	
12.	27	112	118	6	108/70	92/70	16/-	
13.	28	78	84	6	92/64	80/64	12/-	+
14.	36	96	104	8	130/70	122/80	8/-	
15.	37	78	112	34	140/64	108/64	32/-	+
16.	40	76	88	12	140/80	128/90	12/-	
17.	41	76	94	18	106/60	88/60	18/-	+
18.	47	97	110	13	120/90	120/94	-	
19.	48	88	106	18	108/70	100/74	8/-	
20.	49	112	128	16	110/64	110/70	-	
21.	50	92	106	14	180/90	130/70	50/20	
22.	53	88	100	12	114/86	120/92	-	
23.	54	74	88	14	90/70	70/60	20/10	+
24.	55	112	140	28	124/82	86/40	38/42	+

+ = Giddiness present.

abnormal in 1 (14.2%), 2(28.5%), no case, 1(14.2%) and 1(14.2%) case respectively out of 7 patients of peripheral neuropathy.

Abnormalities of sensations were found frequently in patients of peripheral neuropathy due to leprosy . Position sense was impaired in 1(14.2%) case. The appreciation of vibration, touch, pain and temperature were detected abnormal in all cases (100%), 6(85.7%), 6(85.7%) and 6(85.7%) cases respectively. Thickened peripheral nerves (ulnar, popliteal etc.) were found frequently. No autonomic dysfunction was observed in this group of patients.

Duration of symptoms suggestive of peripheral neuropathy may vary from as short as one day to as long as 15 days. in patients of peripheral neuropathy due to Guillain Barre syndrome, when they were attending hospital. The complaint of weakness was found in all cases. Burning was found in 1(16.6%) case out of 6 patients of peripheral neuropathy due to Guillain Barre Syndrome. One case of Guillain Barre Syndrome was associated with porphyria (AIP), an adolescent female.

Areflexia was observed in all the patients of peripheral neuropathy, due to Guillain Barre Syndrome. Power was reduced (Grade 3 and less). Position sense was impaired in all cases. Abnormalities of vibration, touch, pain and temperature were detected in 6(100%), 4(66.6%), 2(33.3%) and 2(33.3%) cases respectively, out of 6 cases

of peripheral neuropathy due to Guillain Barre syndrome. (Table 6). Resting tachycardia was observed in 1(16.6%) case only. Orthostatic hypotension was not detected because patients were unable to stand.

Peripheral neuropathy was asymptomatic in 5 (71.4%) cases out of 7 patients of peripheral neuropathy due to malignancy. Tingling and itching were present in each of remaining 2 cases respectively. Abnormalities in knee, ankle, biceps, triceps and supinator jerks were found in 2(28.5%), 2(28.5%), no case, 1(14.2%) and 1(14.2%) case respectively (Table 5). The jerks were normal in 2 cases (28.5%). Abnormalities in position sense, vibration, touch pain and temperature were found in no case, 4(57.1%), 3(42.8%), 2(28.5%) and 2(28.5%) cases respectively. In 2(28.5%) cases, no sensory abnormality was detected. Resting tachycardia was observed in 1(14.2%) case only.

Out of 11 patients of peripheral neuropathy associated with tuberculosis, 5 patients were having diabetes mellitus (as described above). The remaining 6 patients of peripheral neuropathy are being described here. One patient was also having rheumatoid arthritis and another one patient was also having COAD, in addition to tuberculosis.

Symptoms suggestive of peripheral neuropathy were present in 3(50%) patients out of six patients of peripheral neuropathy due to tuberculosis(and/or anti-

tubercular therapy). Duration of symptoms vary from 1 month to 10 months. Tingling and burning were complained in 2(33.3%) and 1(16.6%) case out of 6 cases of peripheral neuropathy due to tuberculosis and / or antitubercular drugs, malnutrition (Table 4). Abnormalities of knee, ankle, biceps, triceps and supinator jerks were found in 2(33.3%), 4(66.6%), no case, no case and 1(16.6%) case respectively (Table 5). Abnormalities of position sense, vibration, touch, pain and temperature sensations were observed in 1(16.6%), 6(100%), 3(50%), 2(33.3%) and 2(33.3%) cases respectively (Table 6).

Out of 2 cases of peripheral neuropathy due to cirrhosis of liver, one patient complained of numbness in feet for 6 months. This chronic alcoholic patient was having normal tendon jerks, normal position sense but abnormalities in vibration, touch, pain and temperature sensations (loss of these sensations) were found. Another patient of peripheral neuropathy due to cirrhosis of liver was having normal sensation but abnormal biceps, triceps and supinator jerks. Autonomic dysfunction was not observed.

Out of 2 patients of peripheral neuropathy because of COAD and/or malnutrition, one patient had complaint of tingling sensations in hands and feet for one year. In this patient, tendon jerks and position sense were found normal but abnormalities of vibration,

touch, pain and temperature were detected. In another patient of peripheral neuropathy because of COAD and/or malnutrition, ankle jerks were found absent but other jerks and sensations were found normal. Autonomic dysfunction was not found.

One case of peripheral neuropathy due to typhoid fever was having complaint of tingling sensations in hands for one week. In this patient, tendon jerks, position sense, touch, pain and temperature sensations were found normal but 25% loss of vibration sense in hands was found. Autonomic dysfunction was not found.

One case of peripheral neuropathy because of hypothyroidism was having complaints of tingling and numbness in hands and feet for 2 months. In this patient, knee and ankle jerks were found absent. Position sense touch, pain and temperature sensations were normal but patient was unable to appreciate vibration. Other jerks were normal. Autonomic dysfunction was not observed.

D I S C U S S I O N

D I S C U S S I O N

Peripheral neuropathy is a common neurological disorder. No acceptable incidence or prevalence study had been carried out for India, as a whole. However, a report from North-West India gave some information (Kaur et al, 1982). Majority of patients of peripheral neuropathy were having either diabetes mellitus (65.6%) or leprosy (14.4%). Thus in India, diabetes mellitus is a major cause of peripheral neuropathy. In present study, 24(42.85%) cases of peripheral neuropathy were due to diabetes mellitus. This incidence is low as compared to quoted study.

Earlier workers believed that peripheral neuropathy in diabetics was very much related to age of patient, being more common in elderly diabetics (Fundles, 1945; Martin, 1953 and Joslin, 1959). Positive relation between duration of diabetes and peripheral neuropathy is difficult to establish. It would not be legitimate to think that peripheral neuropathy gradually progresses from time of onset of diabetes, as it is well known that many a time patients present initially with neurological complications (Ellenburg, 1970).

Dube et al (1969) found clinical neuropathy in 43 cases out of 80 cases of diabetas mellitus. In present study, all patients of peripheral neuropathy due to

diabetes mellitus were having either symptoms or signs or both, suggestive of peripheral neuropathy, when they attended hospital. This may be due to poor socioeconomic status of patients and / or ignorance about the disease, living in this region. Only 2(8.33%) cases of peripheral neuropathy due to diabetes mellitus were not having symptoms, suggestive of peripheral neuropathy. Tingling and numbness were very common (79.1%). Numbness was always accompanied by abnormal findings on sensory examination. Other symptoms in patients of peripheral neuropathy due to diabetes were giddiness (29.2%), pain (12.5%), weakness (8.3%) and burning (4.1%). Sensory symptoms appeared first at distal part of extremities and then progress proximally giving rise to glove and stocking pattern.

Abnormalities in deep tendon reflexes in patients of peripheral neuropathy, due to diabetes mellitus are very common. Jerks are either reduced or absent. Jerks at distal part of extremities are more commonly abnormal. In present study, ankle and supinator jerks were found abnormal in 83.3% and 58.3% patients of peripheral neuropathy. In patients having long standing diabetes, it may be possible that all jerks of both extremities, bilaterally may be abnormal. In present study, 37.5% patients of peripheral neuropathy due to to diabetes mellitus, all jerks were found abnormal.

Abnormalities of sensations are frequently observed in patients of peripheral neuropathy due to diabetes mellitus.

Distal part of extremities are involved first and with more severity. Loss of vibration sense in lower limbs is very common. In present study, appreciation of vibration was found abnormal in all the patients. Loss of touch sensation in glove and stockings distribution is also common next to vibration sense. We observed abnormalities of touch sensation in 66.6% of patients of peripheral neuropathy. Position sense was impaired in 29.1% of patients of peripheral neuropathy. Both large and small fibre modalities may be involved in diabetic neuropathy. Pain and temperature sensations were found abnormal in 54.1% cases of peripheral neuropathy. Brown, Martin and Asbury (1976) stated that in a group of diabetic patients, small fibre modalities are mostly affected. Pain and temperature sensations are disturbed with relative preservation of position and vibration sense and tendon reflexes are normal or nearly so. In present study, 2(8.33%) cases of peripheral neuropathy due to diabetes mellitus were having abnormal pain and temperature sensations with presence of normal touch and position sense. Excessive hypersensitivity to touch was noted in one patient of peripheral neuropathy, who was complaining of burning feet.

Autonomic dysfunction is often present in diabetic individuals without autonomic symptoms (Pfeifer et al,1982). When autonomic neuropathy is present, damage to vagus nerve may be responsible for resting tachycardia, sometimes as high as 130 beats per minute. The increased resting heart rates in diabetics may be, in some patients, due to cardiac

parasympathetic damage alone and in others due to combined cardiac parasympathetic and sympathetic damage. Since cardiac vagal fibres are generally longer than cardiac sympathetic fibres, they may be more liable to early damage (Ewing et al). We observed tachycardia in supine and standing positions in 4(16.6%) cases and 14(58.3%) cases out of 24 patients of peripheral neuropathy due to diabetes mellitus. Pulse rate of more than 120 per minute was noted in 4(16.66%) cases in standing position. A rise of less than 10 beats per minute, on standing was observed in 9(37.5%) cases. Orthostatic hypotension was found in 6(20.8%) cases of peripheral neuropathy due to diabetes in present study. Giddiness on standing was complained by 7(29.1%) patients.

Slower heart rate (less than 86 beats/minute) of a diabetic with "total cardiac denervation" could be result of both vagal and cardiac sympathetic damage. In present study, 3 patients (12.5%) of peripheral neuropathy due to diabetes had pulse rate of less than 86 beats per minute.

Considering tachycardia, orthostatic hypotension and symptom of dizziness (giddiness) on standing, altogether many patients of peripheral neuropathy due to diabetes mellitus may show at least one of these, as evidence of autonomic dysfunction. We observed autonomic dysfunction in 18(75%) patients of peripheral neuropathy due to diabetes mellitus.

Patients of peripheral neuropathy due to leprosy have more sensory abnormalities as compared to abnormalities in jerks. We observed a case of peripheral neuropathy presented as right sided supraorbital neuralgia for 10 years as also reported by Saxena et al (1990).

Six cases of peripheral neuropathy due to Guillain Barre Syndrome presented with weakness. Sensory symptoms were less marked as compared to motor symptoms. Burning was complained in 1 (16.6%) case only. Abnormalities of vibration sense and position sense were more common, found in 6(100%) cases. Areflexia was found in all cases. One case of peripheral neuropathy due to porphyria (AIP) presented with features of Guillain Barre Syndrome, with areflexia and impairment of position sense, abnormalities in vibration, touch, pain and temperature sensations. This is similar to study of neurological complication in AIP by HC Saxena et al (1986). Resting tachycardia was present in 1 case only.

Patients of peripheral neuropathy due to malignancy were often asymptomatic. We observed asympatomatic peripheral neuropathy in 5(71.4%) cases. Peripheral neuropathy was of mixed sensorimotor type.

Patients of peripheral neuropathy associated with tuberculosis were taking antitubercular drugs. In the present study 11 patients were having tuberculosis. Five patients were having diabetes mellitus also, in whom the causes of peripheral neuropathy may be diabetes.

antitubercular drugs, associated malnutrition or combinations of these. In one case of peripheral neuropathy having tuberculosis and rheumatoid arthritis both, the causes may be antitubercular drugs, associated malnutrition and illness itself. In five cases of peripheral neuropathy, antitubercular drugs and associated malnutrition may be responsible factors for it. Peripheral neuropathy is of mixed sensory-motor type.

Other aetiological factors of peripheral neuropathy, seen were hepatocellular failure (cirrhosis), typhoid, hypothyroidism,chronic alcoholism etc.

Patient of peripheral neuropathy due to typhoid fever was having complaint of tingling sensations with minimal loss of vibration sense and normal jerks and other sensations.

Patient of hypothyroidism was having complaints of tingling and numbness with normal position sense, touch, pain, temperature and abnormalities of jerks and vibration sense.

Possible aetiological factors of peripheral neuropathy in present study were diabetes mellitus(42.85%) leprosy (12.5%), Guillain Barre Syndrome (10.7%), antitubercular drugs, malignancy, cirrhosis of liver, COAD, typhoid, hypothyroidism, rheumatoid arthritis, chronic alcoholism, Buerger's disease, porphyria and associated malnutrition. Two (8.33%) cases of peripheral neuropathy

due to diabetes were asymptomatic. All cases of peripheral neuropathy due to leprosy and Guillain Barre syndrome were symptomatic. Five patients (71.4%) of peripheral neuropathy due to malignancy were asymptomatic. Three (50%) patients of peripheral neuropathy associated with tuberculosis were asymptomatic.

SUMMARY AND CONCLUSION

SUMMARY AND CONCLUSION

Peripheral neuropathy is a common neurological disorder. Present work "A clinical study of peripheral neuropathy in Bundelkhand region" was carried out in the Department of Medicine, M.L.B. Medical College, Hospital, Jhansi. Fifty six consecutive patients of peripheral neuropathy due to different causes were studied. Following conclusions could be drawn from our study :

1. Aetiological factors, found, were diabetes mellitus in 24 (42.85%) cases, Leprosy in 7(12.5%) cases, Guillain Barre syndrome in 6(10.7%) cases, tuberculosis (with antitubercular drugs) in 11 cases and malignancy in 7(12.5%) cases. Other uncommon causes detected were cirrhosis, COAD, typhoid, hypothyroidism, rheumatoid arthritis, Buerger's disease, chronic alcoholism, porphyria and associated malnutrition in many of these cases.

2. Asymptomatic peripheral neuropathy was detected in 2(8.33%) cases due to diabetes mellitus, 5(71.4%) cases due to malignancy, 3(50%) cases due to tuberculosis (with antitubercular treatment and without having diabetes).

3. Few cases of peripheral neuropathy were having two or more diseases (associations). Five patients of periperhal neuropathy with diabetes mellitus were also

having tuberculosis. One patient of peripheral neuropathy was having tuberculosis and rheumatoid arthritis both. One patient of peripheral neuropathy with diabetes mellitus was also having Buerger's disease. One patient of peripheral neuropathy with tuberculosis was chronic alcoholic. One patient of peripheral neuropathy with cirrhosis of liver was chronic alcoholic. One patient of porphyria (AIP) presented with feature of Guillain Barre Syndrome.

4. We observed autonomic dysfunction in 18(75%) patients of peripheral neuropathy due to diabetes mellitus.

5. In patients of peripheral neuropathy due to leprosy sensory abnormalities are more commonly observed as compared to abnormalities in jerks.

6. One patient of peripheral neuropathy due to leprosy presented with symptoms suggestive of right sided supraorbital neuralgia. Thus leprosy may present primarily with involvement of cranial nerves.

7. Areflexia is a common finding in patients of peripheral neuropathy due to Guillain Barre Syndrome.

8. Porphyria (AIP) may present as Guillain Barre Syndrome.

B I B L I O G R A P H Y

B I B L I O G R A P H Y

Abhayambika K et al : Peripheral neuropathy and haemolytic anaemia with cherry red spot on macula in dapsoe poisoning. JAPI, 1990; 38(8) : 564-65.

Adlakha A, Phillip PJ, Dhar KL, :Guillain-Barre syndrome as a sequela of organophosphorus poisoning. JAPI 1985;665-7.

Argov Z and Mastaglia FL : Drug induced peripheral neuropathies, B M J, 1979; 1 : 663.

Asbury AK : A text book on peripheral neuropathy.

Asbury AK, Johnson PC : Pathology of peripheral nerves. Philadelphia W.B. Saunder Co, 1978; Chapter 5.

Barraclough MA , Sharpey-Schafer EP : Hypotension from absent circulatory reflexes. Lancet, 1963; i : 1121-26.

Casey EB et al : Vincristine neuropathy, clinical and electrophysiological observations. Brain, 1973;96:69-73.

Cavanagh JB, Mellick RS : On the nature of the peripheral nerve lesions associated with acute intermittent porphyria. J Neurol Neuro Surg-Psychiat 1965; 28 : 320-27.

Cavangh NPC et al : Hereditary sensory neuropathy with spastic paraplegia. Brain 1979; 102 : 79.

Chuttani PN : Peripheral neuropathies. JAPI 1968; 16:265-70.

Chuttani PN, Chawala LS, Chugh KS, Singh H : Landry Guillain Barre - Strohi Syndrome in India. J Neurol Sic, 1968; 7 : 581-92.

Chuttani PN : Peripheral neuropathies. JAPI 1968; 16:265-70.

Clark BE et al : The natural history of diabetic autonomic neuropathy. Quart J Med 1980; 49 : 95.

Clark BE : Diagnosis and management of diabetic autonomic neuropathy. Brit Med J 1982; 295 : 916.

Clements RS Jr, Bell DS : Diabetic neuropathy - peripheral and autonomic syndromes. Post grad Med 1982; 71 : 60-7.

Croft PB, Urich H, Wilkinson M : Peripheral neuropathy of sensori-motor types associated with malignant disease. Brain 1967; 90 : 31-66.

Dube BK, Mathur KS, Luthra UK and Singh CJ : Neurological manifestations in diabetes. JAPI 1969; 17 : 33-40.

Edmonods ME, Archer AG, Watkins PJ : Ephedrine, a new treatment for diabetic neuropathic edema. The Lancet March 12, 1983 : 548-550.

Ewing DJ, Campbell JW, Burt AA and Clarke BF : Vascular reflexes in diabetic neuropathy. Lancet 1973; 2 : 1354-56.

Ewing DJ et al : Mortality in diabetic autonomic neuropathy. Lancet 1976; i : 601-03.

Ewing DJ, Campbell IW, Murray A, Neilson JMM, Clarke BE : Immediate heart rate response to standing : simple test for autonomic neuropathy in diabetes. Bri Med J 1978; 1 : 145-147.

Ewing DJ, Campbell IW, Clarke BF : Assessment of cardiovascular effect in diabetic autonomic neuropathy and prognostic implications. Ann Intern Med 1980; 92 : 308-11.

Ewing DJ, Campbell IW, Clarke BF : Heart rate changes in diabetes mellitus. The Lancet, Jan 24, 1981; 183-85.

Gupta OP, Agarwal BL, Kumar N : Guillain Barre syndrome : A report of 116 cases. JIMA, 1982; 78 : 43-7.

Gupta OP et al : Clinical profile and electrodiagnostic study of peripheral neuropathy. JAPI 1989; 37 (9) : 578-82.

Greene DA, Lattimer SA, Sima AF : Sorbitol phosphoinositides and sodium potassium ATPase in the pathogenesis of diabetic complications. N Engl J Med 1987; 316 : 599-606.

Harrison's Principles of Internal Medicine, 12th ed.

Jharakan J, Jayprakash PA, Padmanabha Iyer V : Small volume plasma exchange in Guillain Barre Syndrome, Experience in 25 patients. JAPI 1990; 38(8) : 550-553.

Kumar BR, Gill HS : Motor nerve conduction velocities and neuropathy amongst diabetics. JAPI 1988; 36(10) : 589-593.

Locke S : The peripheral nervous system in diabetes mellitus. Diabetes 1964; 13 : 307.

Low PA, Walsh JC et al : The sympathetic nervous system in alcoholic neuropathy. A clinical and pathological study. Brain 1975; 98 : 357-64.

Low PA, Walsh JC, Huang CY and Mcleod JC : The sympathetic nervous system in diabetic neuropathy - a clinical and pathological study. Brain 1975; 98 : 341.

Low PA, Walsh JC et al : The sympathetic nervous system in alcoholic neuropathy : A clinical and pathological study. Brain 1975; 98 : 357.

Martin M : Involvement of autonomic nerve fibres in diabetic neuropathy. Lancet 1953; 1 : 560.

Mc Farland HR, Heller GI, Arbor A : The Guillain Barre disease complex - A statement of diagnostic criteria and analysis of 100 cases. Arch Neurology, 1966; 14 : 197-201.

Menon GN : Diabetic neuropathy, some relevant facts. IGCP, Diabetes January 1992; p 63-66.

Mohan R, Mohan V, Ramchandran A, Viswanathan M : Retinopathy in insulin dependent diabetes mellitus (IDDM) in South India. JAPI 1988; 36(12) : 703-705.

Mohan V, Ramchandran A, Shivkumar VK and Viswanathan M : Diabetic autonomic neuropathy - clinical evaluation J Diab Asso India 1980; 20 : 69-71.

Mulder DW, Lambert EH, Bastrom JA : The neuropathies associated with diabetes mellitus - a clinical and EMG study of 103 unselected cases. Neurology (Minneap) 1961; 11 : 275-84.

Nath AR, Mehta PJ, Bichile SK, Sainani GS : Porphyrias and neurological disease. JAPI 1988; 36 : 581-582.

Page MM, Watkins PJ : Cardiorespiratory arrest and diabetic autonomic neuropathy. Lancet 1978; i : 14-16.

Raman PG : Interesting observation in the treatment of diabetic sensory neuropathy. JAPI 1989; 37(3) : 245.

Rollo : cited by Martin M : Diabetic neuropathy, a clinical study of 150 cases. Brain 1953; 76 : 594.

Rundles R : Diabetic neuropathy general review with report of 125 cases. Medicine 1945; 24 : 111-60.

Samal KK, Sahu CS : Organophosphorus poisoning and intermediate neurotoxic syndrome. JAPI 1990; 38(2) : 181-182.

Saxena S, Gupta R, Nigam DK, Singh KG, Saxena KN : Multiple cranial nerve involvement with probable trigeminal neuralgia in leprosy. JAPI 1990; 38(10) : 802-803.

Saxena HC, Malhotra H, Mathur SN : Neurological complications in intermittent acute porphyria. JAPI 1988; 36 (10) : 585-588.

Senanayake N, Karalliedde L : Neurotoxic effects of organophosphorus insecticides - "An intermediate syndrome. New Engl J Med 1987; 316 : 761-3.

Seshiah V et al : Treatment of diabetic subjects with sensory neuropathy. JAPI 1988; 36(8) : 527-528.

Shiddharth N Shah : Diabetic nephropathy - a continuing challenge. JAPI 1990; 38(11) : 829-830.

Singh MM, Singh Ram, Goyal SP, Singh SP et al : Antiautonomic nerve antibodies in autonomic neuropathy in diabetes mellitus. JAPI 1988; 36 (3) : 197-200.

Singh N, Sachdev KK : Peripheral neuropathies in; Ahuja MMS Ed. progress in clinical medicine in India 2nd ed. New Delhi Arnold - Hereman Publishers 1981; 241-80.

Subhedar BJ, Markand ON : Neurological manifestations of acute intermittent porphyria. JAPI 1963; 11 : 1045-52.

The Lancet : Hypoglycaemic peripheral neuropathy. Lancet, 1982 ; ii : [illegible]1447.

The Lancet : Influenzae and the Guillain Barre syndrome. Lancet, 1984; ii : 850.

Thrugh DC : Congenital insensitivity to pain - a clinical genetic and neurophysiological study of four children from the same family. Brain 1973; 96 : 369.

Wadia PZ : Retrobulbar neuritis in two patients with falciparum malaria. JAPI 1990; 38(10) : 800-801.

Watkins PJ : Facial sweating after food, a new sign of diabetic autonomic neuropathy. Br Med J 1973; i : 583.

Wheeler T, Watkins PJ : Cardiac denervation in diabetes. Brit Med J 1973; iv : 584-86.

Zohar A, Frank LM : Drug induced peripheral neuropathy. Brit Med J 1979; 1 : 663-666.

Peripheral

Master Chart Showing ~~Of~~ 56 Patients Of ~~Peripherals~~ Neuropathy

Abbreviations :-

R = Reduced
A = Absent
N = Normal

Patient No.	Age Years	Sex	Complaints With Duration	Pulse Supine	Pulse Standing	BP Supine	BP Standing	Reflexes Pupillary	Cremasteric	Plantar	Knee Jerk	Ankle Jerk	Biceps	Triceps	Supinator	Sensations and Others	Association
1.	48	M	* Burning Feet-16 Years (Plantar Surface) * Tingling Sensation over dorsum of feet-16 years * Pain in calf muscles on walking -- 16 years * Diminution of vision -- 16 years	96	112	180/110	156/82	N	N	N	L-R R-N	L-A R-A	N	N	L-A R-A	Position Sense-N Vibration-Lost both extremities bilaterally Touch -- N Pain -- N Temperature	Diabetics melitus (IDDM) with Retinipathy
2.	13	M	* Increased appetite * Increased urination * Tingling sensations lower limbs * Loose motions (off and on) ------- 2 years * Pain calf muscles bilaterally ------- 6 months	84	90	120/100	120/100	N	N	N	L-A R-A	L-A R-A	L-A R-A	L-A R-A	L-A R-A	Positon sense - N Vibration - lost both extremities bilaterally Touch -- N Pain -- N Temperature -- N	Diabeties Mellitus (IDDM) with anaemia
3.	56	M	* Generalised weakness * Increased urination * Increased appetite * Tingling sensations over toes of lower limbs ------1 year	78	82	110/82	108/82	N	N	N	N	N	N	N	N	Position sense - N Vibration - lost both extremities Touch - increased sensations about one and half times normal over the toes and dorsum of feet upto area of metatarsals, bilaterally Pain -- N Temperature -- N	Diabeties Mellitus (IDDM) with anaemia with tobacco chewing (40 years)
4.	62	M	* Rashes and ulcers on both upper and lower extremities -- 5 months	82	90	134/76	134/80	N	N	N	N	N	N	N	N	Position sense - N Vibration -lost both upper and lower extremities and over erythematous patches	Leprosy with tobacco smoking (40 years)

																over trunk Touch - Reduced about 60% over erythematous patches Pain - Reduced about 80% over erythematous patches Temperature - Reduced about 80% over erythematous patches others - Thickened and tender ulnar and poppliteal nerves bilaterally.	
5.	25	M	* Patches over lower limbs ---- 18 years * Loss of sensations Lower limbs – 10 years * Loss of sensation Right Forearm and hand – 10 years * Loss of sensation left hand — 2 1/2 years * Unable to extend fingers of Right hand — 1 year	80	84	112/70	110/72	N	N	N	N	N	N	L-N R-A	L-A R-A	Position sense - N Vibration- absent in in lower limbs 50% loss in right upper limb Touch- 75% loss over lower limbs right forearm and left hand and over hypopigmented patches over the chest Pain- 100% loss over lower limbs right forearm and left hand and over hypopigmented patches over the chest Temperature- as for pain Others- Thickened and tender ulnar and poppliteal nerves bilaterally and left greater auricular nerve. Fixed flexion deformity of 3rd, 4th, 5th fingers of right hand	Leprosy with anaemia
6.	40	M	* Reduced sensations over feet and hands ---- 7 years	74	80	124/80	128/82	N	L-A R-A	N	N	N	N	N	N	Position sense-N Vibration - 100 % loss over both lower limbs, both hands and forehead Touch- 100% loss below knee joints and below mid of thighs, 100% loss over both hands. Pain- 100% loss both lower limbs below mid of thighs 100% loss over both hands Temperature- same as for pain Others- Thickened and	Leprosy (LL with severe ENL) with tobacco smoking (12 years)

																tender ulnar nerves and thickened non tender poppliteal nerves bilaterally.	
7.	40	M	* Pain right half of head * Numbness in Left 5th fingr - 1 year and 4 month * Tingling sensation in both Forearms and hands - 20 days * Swelling of both wrists joints and over Supraorbital region of Forhead — 15 days	76	80	128/78	124/78	N	N R-A	N	N	L-A R-A	N	N	N	Position sense- N vaibration-absent in right and left hands and right lower limb below knee joint. Tuch 100% loss both right and left hands 50% loss right foot (dorsum and outer four toes). Pain - 100% Loss both Right and Lefthand, 50% Loss over Right Foot (dorsum and outer four toes,25% Loss both forearm and Right Lower Leg. Temp - as fer pain Others - Tender and thickened supraorbital nerves, Right great auricular nerve, ulnar nerves,common peroneal nerves.	Leprosy(BL) with tobacco smoking and chewing 20 yrs.
8.	50	M	Hypopigmented patch at right elbow joint (extensor aspect)1 1/2 months * Numbness Right hand 1 1/2 months.	74	78	128/78	130/80		N	N	N	N	N	N	N	Position Sense - N Vibration-100% Loss in both lower limbs, Right upper limb and and over scalp and face Tuch - 75% Loss over hypopigmented patches and over left patches. Temp - 100% Loss over hypopigmented patch. Others - Poppliteal nerves are thicked and nontender, Hypopigmented patches are present over back and chest.	Leprosy (BB)
9.	45	M	Non healing ubcers at at right lower chest (lateral) * Non healing ulcers at left forearm(extensor-	82	86	120/72	120/74	N	N	N	N	N	N	N	N	Postion sense -N vibration 50% loss over right hand Touch-N Pain -N	Leprosy(LL)

			aspect 7 months)													Temp -N Others- Popplitealnerves thickned and tender, ulnar nevers thickened and nontender	
10.	25	M	* Hypopigmented patch over left knee joint-3 years * unable to extend right foot -1 year * Ulcer over right foot (planter aspect- 6 months)	78	80	118/78	118/78	N	N	L-N R-A	L-A R-A	L-A R-A	N	N	N	Postion sense-impaired vibration-100% loss both upper and lower limbs Touch-50% loss over hypopigmented path and lower limbs Pain- 100% loss over hypopigmented patch and both lover limbs. Temp- as for pain Others-Ulner nerves and poppliteal nerves are thickened and tender	Leprosy
11.	55	M	* Cough with expectoration 1 1/2 years * Tingling sensation both feet and hands(off and on) 10 months	82	84	124/82	124/80	N	N	N	N	L-A R-N	N	N	L-A R-A	Postion sense - N Vibration- 100% loss in left foot, 25% loss in Right foot, 25% loss in left and righthands. Touch- 50% loss in left feet Pain-N Temp-N	Pulmonary Tyberculogis with ATT(11 months)
12.	26	F	*Increased appetite, thirst and urination-3 years. *Tingling sensations in feet and hands - 1 year * Pain in chest and back 15 days	110	122	130/88	112/90	N	N	N	N	N	N	N	N	Position sense-N Vibration-75% loss in feet, 25% loss in upper limbs Touch -N Pain - N Temp - N	Diabetes mellitus
13.	60	F	*Swelling over feet and face - 6 months * Cough with expectoration * Fever off and on * Loss of appetite - 4 months * Tingling sensations over lower limbs and upper limbs 3 months	104	118	90/74	82/74	L-NE R-N	-	N	N	L-R R-A	N	N	N	Position sense - N vibration - 100% loss in lower limbs, 50% loss upper limbs Touch - N Pain - N Temp - N Others-Both knee joint are swollen, Flexion deformity of fingers of both hands, left eye destroyed (? small pox at age of 5 years), Right sided pleural effusion, Impaired function of 8th nerve on both sides.	Rheumatird arthritis (20 years) Pulmonary Tuberculoses (4 months) ATT (2 months)

14.	40	M	* Weakness lower limbs 2 days. * Weakness upper limbs 1 day * Retention of urine 1 day	82	-	104/64	-	N	L-A R-A	L-A R-A	L-A R-A	L-A R-A	L-A R-A	L-A R-A	L-A R-A	Position sense-impaired vibration-Patient is unable to appreciate it. Toouch - 25% loss distal to knee joints in lower limbs Pain - N Temp _ N	Guillain Borre Syndrome
15.	45	F	* Increased oppetite * Increased urination 6 years. * Tingling sensations in feet and hands - 3 years * Breathlessness off & on 3 years * Swelling feet 1 1/2 months	94	108	118/72	94/70	N	-	N	L-A R-A	L-A R-A	N	L-A R-A	L-A R-A	Position sense -N Vibration - 75% loss below knee joints,75% loss below wrist joints Touch- 50% loss below ankle joints and wrists joints Pain - 50% loss below ankle joints and wrist joints Temp - as for pain Others - Myocardial inforction (anterior wall)about 2 1/2 years back, Bilateral pleural effusion present.	Diabetes mellitus with FUC of Myocardial infarction (ant.wall) with CHF
16.	50	M	* Fever off and on * Increased urination * Burning micturition 1 year * Increased appetite and thirst - 8 months	88	94	102/72	100/72	N	L-A R-A	N	N	N	N	N	N	Position sense - N Vibration - 100% loss both extremities bilaterally Touch - N Pain - N Temp - N Others- Tuberculosis Right lung	Diabetes mellitus with Koch's lung with Tobacco (chewing and smoking)for 30 years
17	42	M	* Increased urination * Increased thirst * Increased appetite 5 years * Weakness - 4 months * Diminution of vision (both eyes) 1 months	90	112	192/112	130/92	Slug gish	L-A R-A	N	N	L-A R-A	N	N	N	Position sense - N Vibration - 100% loss below elbow joints and and ankle joints and over head. Touch - 100% loss of fine touch below elbow joints and ankle joints Pain- 50% loss below elbow joints and ankle joints Temp - 50% loss below elbow joints and ankle joints Others - Retinopathy(grade	Diabetes mellitus with Anaemia with Tabacco smoking for 20 years.

																3rd) present.	
18.	60	M	* Increased urination * Increased appetite * Increased Thirst 2 years * Cough with expectration 1 1/2 years * Unable to walk 1 1/2 years	96	122	110/62	82/60	N	L-A R-A	N	L-R R-N	L-A R-A	N	N	L-A R-A	Position Sense-N Vibration-100% Loss in feet and hands, 50% in Forearms and Leg below knee joints Touch - N Pain-50% Loss in hands and feet. Temp-50% Loss in hands and feet. Others-Left pyopneumothorax.	Diabetis mellitus Tuberculosis of lung with left pyopneumothorax with anaemia with irregular ATT (1 year) with Tabacco smoking (30 years).
19.	18	M	* Headache-15 years * Fever off & on 15 days	76	78	122/70	120/72	N	N	N	L-A R-A	N	N	N	N	Position - N Vibration - N Touch - N Pain - N Temp - N	FUC of Hodgekin's disease (defected 6 months back & Rx with Mopp)
20.	60	M	* Cough with expectoration * Fever off & on 15 days	82	84	110/72	108/68	N	L-A R-A	N	N	N	N	N	N	Position - N Vibration - N Touch - N Pain - N Temp - N	COAD ~~of~~ with CML (defected 1 month back) with Tabacco chaing (5 years).
21.	30	F	* Unable to stand - 1 day * Workness upper limbs 1 day	94	-	106/60	-	N	-	L-A R-A	L-A R-A	L-A R-A	L-A R-A	L-A R-A	L-A R-A	Position Sense-Impaired Touch - N Pain - N Temp - N Vibration - Unable to appreliate.	GUillain Barre Syndrome
22.	32	M	* Fever (off & on) * Cough with expectoration * Loss of weight * Loss of appetite 1 year	82	90	106/70	104/70	N	N	N	N	L-A R-A	N	N	N	Position Sense- N Vibration-100% Loss in upper and lower extremities bilaterally. Touch - 50% Loss below knee joints, 40% Loss below wrists joints. Pain - 25% Loss below knee joints. Temp - 25% Loss below knee joints.	Pulmonary Tuberculosis (extensive) with anaemia.
23.	45	M	* Increased urination * Increased appetite * Increased Thirst 1 year * Tingling sensation in	74	80	134/100	98/74	N	L-A R-A	N	N	L-A R-A	N	L-A R-A	L-A R-A	Position Sense- N Vibration-Patient is unable to appreciate Touch- fine touch is loss over feet and hands	Diabetes mellites with anaemia

			* feet and hands 2 1/2 months													Pain - 50% loss over feet and hands. ~~Temp-50% loss over feet and hands.~~ Temp - as for pain	
24.	F		* Increased urination * Increased appetite * Increased Thirst * Tingling Sensation feet & hands-9 months * Pain abdomen-6 months	84	90	116/80	118/80	N	-	N	L-A R-A	L-A R-A	L-A R-A	L-A R-A	L-A R-A	Position Sense-Impaired Vibration-100% Loss over feet & hands,75% Loss over rest area of extremities. Touch - Crude - 100% Loss over toes & finger,50% Loss over rest area of feet & hands. Fine- 100% Loss over feet & hands,50% Loss below knee & elbow joints. Pain - Superficial- 100% Loss over toes of feet & fingers of hands ,75% Loss over rest area of feet & hands. Temp - as for Pain	Diabetes mellites with Koch's abdomen
25.	42	M	* Pain calfmuscles on walking - 10 months * Non healing ulcer at Lefthands - 5 months	86	88	128/82	110/82	N	N	N	N	L-A R-A	N	L-A R-A	N	Position Sense- N Vibration-100% Loss over feet & hands,60% Loss over area below knee & elbow joints. Touch-100% Loss in Second Third toes of left foot, 50% Loss in rest area of feet & hands. Pain-100% Loss in Second Third tose of left foot, 75% Loss in rest area of feet & hands, 50% Loss below knee & elbow joints. Temp- as for pain	Diabetis mellitus with Buerger's disease with non healing ulcer at left heal. with Tabacco smoking (15 years)
26.	38	M	* Distension of abdomen 1 year * Sensation of Numbness feet - 6 months	88	96	128/78	108/60	N	N	N	N	N	N	N	N	Position - N Vibration-15% Loss in feet. Touch-15% Loss below ankle joints & below mid of forearms & in hands. Pain-15% Loss below ankle joints & hands. Temp - Hot-25% Loss below ankle joints, 25% Lossdistal to mid of	Cirrhosis with alcohol consumption (20 years) with Tabacco smoking (20 years)

																forearms & hands(Right side), 40% Loss distal to mid of forearms and hands(left side). Cold-15% Loss distal to ankle joints & mid of forearms and in hands.	
27.	25	F	* Increased urination * Increased thirst * Increased appetite 1 year * Tingling sensation in feet, hands and legs 5 months * Wound in Right hand (after thorn prick) 15 days	112	118	108/70	92/70	N	-	N	N	L-A R-A	N	N	L-A R-A	Position sense - N vibration - 50% loss distal to elbow joints 100% loss distal to knee joints. Touch - Crude - 50% loss distal to to knee joints, and elbow joints. Fine - 100% loss distal to knee joints, 50% loss distal to elbow joints. Pain -50% loss below knee and elbow joints. Temp -50% loss below knee joints and elbow joints. Others - cataraet in left eye	Diabetes mellitus
28	70	M	* Increased urination * Increased appetite * Increased thirst 2 years * Tingling sensations lower limbs - 2 years.	78	84	92/64	80/64	N	L-A R-A	N	N	L-A R-A	N	N	N	Position sense - N vibration - 100% loss both lower limbs and upper limbs. Touch - N Pain - N Temp - N	Diabetes mellitus with tabacco smoking (40 years)
29	42	M	* Fever - 6 months * Pain all over body 6 months * Swelling at groins and neak - 5 months.	112	114	118/54	110/50	N	N	N	N	L-A R-A	N	N	L-A R-A	Position sense - N Vibration - unable to appreciate Touch - Fine touch is 25% lost in feet. Pain - N Temp - N	Acute myeloblastic Leukaemia (AML - M1)
30	35	M	* Weakness - 18 months * Pain abdomen 18 months * Fever (off & on) 18 months.	76	80	110/70	100/72	N	L-A R-A	N	N	N	N	N	N	Position sense - N Vibration - 75% loss distal to knee joints 25% loss distal to elbow joints. Touch - 25% loss in feet Pain - 25% loss in feet Temp - 25% loss in feet.	Non hodgekin Lymphona (large cell type) with tabacco smoking (20 years)

31	37	F	*Fever with chills 15 days *Vomiting(once or twice daily 15 days. * Tingling sensations in hands 1 week.	82	88	110/70	112/72	N	-	N	N	N	N	N	N	Position sense - N Vibration 25% loss in hands distal to wrist joints. Touch - N Pain - N Temp - N	Typhoid
32	45	M	* Breathlessness-3 Years * Tingling sensations hands and feet -1 year	88	94	110/72	120/82	N	N	N	N	N	N	N	N	Position senxe- N Vibration-100% loss extremities bibate- rally. Touch-75% Loss distal to elbow joints & knee joints. Pain- 75% Loss distal to elbow joints and knee joints Temp- 75% Loss distal to elbow joints and knee joints.	COAD with malnutrition with Tobacco Smoking (20 years)
33	60	F	*Yellow discolbouration of conjunctivae *Swelling abdomen *Itching senstions all over body -4 Months	62	68	108/72	110/74	N	-	N	N	L-A R-A	N	N	L-A R-A	Position Sense-N Vibration-100% Loss over both extremit- ies bilaterally. Touch-25% Loss distal to knee joints & elbow Joints. Pain-25% Loss distal to to knee and elbow joints Temp-25% Loss distal to knee & elbow joints	Carcinoma Head of the pancreas
34	23	M	* Swelling in abdomen (Left side) --1 year * Tingling sensations Feet and hands ---3 Months	84	90	114/64	112/64	N	N	N	N	N	N	N	N	Position sense-N Vibration-100% Loss distal to knee joints & elbow joints Touch-N Pain-N Temp - N	CML
35	45	F	* Breathlessness (off& on) *Cough c expectoration (off & on) --4 years *Fever -4 days	62	68	110/72	108/72	N	-	N	N	L-A R-A	N	N	N	Position sense -N Vibration-N Touch -N Pain-N Temp -N	COAD
36	47	F	*Tingling & numbness over feet hands -3 months *Loose motions --2 days	96	104	130/70	122/80	N	-	N	L-A R-A	L-A R-A	L-A R-A	L-A R-A	L-A R-A	Position Sense- Impaired Vibration-100% Loss in in both extremities bilaterally Touch-100% Loss about one inch proximal to ankel joints and feet, 75% Loss about one inch	Diabetes Mellitus

																proximal to wrist joints and hands Pains--50% Loss just above ankle joints and feet and just proximal to wrist joints and hands. Temp -as for pain Others -Retinopathy present	
37	50	M	* Increased urination * Increased appetite * Increased thirst --1 Year *Tingling and numbness sensation feet and hands --1 Year *Giddiness --6 months * Cough with expectoration ----6 Months	78	112	140/64	108/64	N	L-A R-A	N	N	N	N	N	N	Position sense-N Vibration-100% Loss Lower extremities, 100% Loss distal to elbow Touch-15% Loss from six inch Proximal to ankle joints upto whole of feet, bilaterally Pain-N Temp -N	Diabetes Mellitus With Pulmon- ary tuberculosis with Tobacco smoking (35 years)
38	60	M	*Cough ē expectoration (off & on) * Burning sensations lower Limbs and hands --1 Month * Fever -10 days	74	84	110/70	92/60	N	L-A R-A	N	N	N	N	N	N	Position sense -N Vibration -100% Loss in Lower Limbs and hands Touch -N Pain-20% increased sensation distal to joints ,bilaterally Temp-20% increased sensation distal to knee joints, bilaterally	COAD with Pulmonary Tuberculosis with alcohol consumption (40 years) and tobacoo smoking and chewing (40 years)
39	60	F	* Pain abdomen - 1 day * Unable to stand -1 day * Weakness upperlimbs - 1 day * Retention of urine -6 hours	104	-	96/70	-	N	-	L-A R-A	L-A R-A	L-A R-A	L-A R-A	L-A R-A	L-A R-A	Position sense-impaired Vibration-patient is unable to appreciate it. Touch-50% Loss in Lower & 25% Loss in upper limbs Pain-50% loss in Lower Limbs, 25% Loss in upper Limbs Temp-as pain.	Guillain Barre syndrome with porphyria
40	60	F	* Tingling sensations distal to both knee joints --2 years	76	88	140/80	128/90	N	-	N	L-A R-A	L-A R-A	L-R R-A	L-A R-A	L-A R-A	Position sense-N Vibration- Patient is unable to appreciate Touch -50% Loss distal to knee joints bilaterally Pain- N Temp - N	Diabetes Mellitus
41	55	M	* Increase urination * Increased Thirst * Increased appetite ---6 years * Giddiness on Standing	76	94	106/60	88/60	N	L-A R-A	N	N	L-R R-A	N	L-A R-A	N	Position Sense -Impaired Vibration-100% loss in extremities,bilaterally. Touch- 75% loss distal to knee joint in Right	Diabetes mellitus with CAD with Tabacco chewing

			----5 years * Chest pain on exertion * Breathlessness on exertion ---- 3 years * Tingling and numbness sensations upper & lower limbs ---1 year													Lower limb ,50% Loss distal to knee joint in left lower limb,25% loss distal to elbow joint in Right upper limb,25% Loss distal to elbow joint in left upper limb, Pain- 50% Loss distal to knee joints,25% Loss distal to elbow joints . Temp- as for pain.	(40 years)
42	50	M	* Distension of abdomen * Cough c expectoration -----3 Months * Swelling feet ---1 Month	92	102	100/72	98/70	N	N	N	L-R R-A	N	N	N	N	Position sense -N Vibration-100% Loss in both extremities, bilaterally. Touch- N Pain-N Temp-N	Pulmonary tuberculosis with ascites with anaemia with Tobacco smoking (30 years).
43	16	M	*Weakness Lower limbs ----15 days *Weakness upper limbs ---15 days	78	-	100/70	-	N	L-A R-A	L-A R-A	L-A R-A	L-A R-A	L-A R-A	L-A R-A	L-A R-A	Position sense-Impaired Vibration- Patient is unabel to appreciate it. Touch- 50% Loss in both extremities bilaterally Pain-25% loss in both extremities(B/L) Temp- as for pain.	Guillain Barre syndrome
44.	24	M	* Fewer with chills & rigor for 3 days --1 month back * Pain abdomen-15 days * Nodular swelling in neck axillae, inguinal regions --15 days	82	88	124/80	120/80	N	N	N	L-A R-A	N	N	N	N	SENSORY SYSTEM- NORMAL	Hodgekin's Lymphoma
45	45	M	* Distension of abdomen ---3 Months	76	82	102/60	98/60	N	L-A R-A	N	N	N	L-R R-A	L-R R-N	L-R R-N	Sensory system-Normal	Cirrhosis of liver with ascites with anaemia with Tobacco Smoking (30 Years).
46.	30	M	* Burning sensation feet ----3 days *Weekness Lower Limbs -----1 days	92	-	122/84	-	N	L-A R-A	L-A R-A	L-A R-A	L-A R-A	L-A R-A	L-A R-A	L-A R-A	Position Sense-Impaired Vibration-Patient is unable to appreciate it. Touch-25% Loss in feet Pain - N Temp - N	Guillain Barre Syndrome
47.	30	M	* Increased Urination	97	110	120/90	120/94	N	L-A	L-A	L-A	L-A	L-A	L-A	L-A	Position Sense-Impaired	Diabetes

			* Increased Thirst * Increased appetite ---15 months * Tingling & numbness sensation feet & Legs ---- 8 months * Tingling & Numbness sensation in hands -- 1 month						R-A	R-A	R-A	R-A	R-A	R-A	R-A	Vibration-Patient is unable to appreciate Touch-100% Loss distal to mid of thighs in lower limbs,25% loss distal to elbow joints bilaterally Pain-25% Loss In feet & hands bilaterally. Temp- 25% Loss in feet & hands bilaterlly.	mellitus
48.	18	M	* Increased Urination * Increased Thirst * Increased appetite * Diarrhoea -- 4 months * Tingling Sensation in feet & hands -- 1 month	88	106	108/70	100/74	N	N	N	L-A R-A	L-A R-A	L-A R-A	L-A R-A	L-A R-A	Position Sense- Impaired Vibration-Patient Is unable to appreciate vibration sense. Touch-25% loss in feet & bilaterally. Pain - N Temp - N	Diabetes mellitus (IDDM)
49.	35	F	* Increased Urination * Increased Thrist * Increased appetite * Tingling & Numbness Sensations in lower limbs distal to knee joints -- 8 months	112	128	110/64	110/70	N	-	L-A R-A	L-A R-A	L-A R-A	L_A R-A	L-A R-A	L-A R-A	Position Sense-Impaired Vibration-patient is unable to appriciate vibration sense. Touch - 25% Loss distal to knee joints,bilaterally Pain - N Temp - N	Diabetes mellitus
50.	60	F	* Known case of Diabetes 15 years * Known case Of Hypert~~ation~~ension -- 1 1/2 years * Cough with ~~expecoration~~ expectoration -- 3 months * Fever 1 month	92	106	180/90	130/70	N	-	N	N	L-A R-A	N	N	N	Position Sense- N Vibration-Patient is unable to appriciate vibration sense. Touch - N Pain - N Temp - N	Diabetes mellitus wtih Hyper~~tantion~~tension with pulmonary tuberculosis
51.	22	F	* Fever ---2 days * Bodyache --2 days * Weekness lower Limbs & upper limbs -- 1 day	76	-	104/68	-	N	-	L-A R-A	L-A R-A	L-A R-A	L-A R-A	L-A R-A	L-A R-A	Position Sense- Impaired Vibration-patient is unable to appreciate vibration sense. Touch - N Pain - N Temp - N	Guillain Barre Syndrome
52.	25	F	* Cough with expectoration * Fever * Weightloss -- 2 years	122	140	112/70	90/70	N	-	N	L-R R-R	L-A R-A	N	N	N	Position sense- Impaired Vibration - patient is unable to appreciate vibration sense. Touch -50% Loss distal to knee joints bilaterally. Pain - N Temp - N	Pulmonary tuberculosis with irregular ATT (2 years)